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BULLETIN

OF THE NEW YORK ACADEMY OF MEDICINE

Original Articles by

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J. LAWRENCE POOL

IATROGENICALLY INDUCED LIVER DISEASE

Transcription of a Panel Meeting

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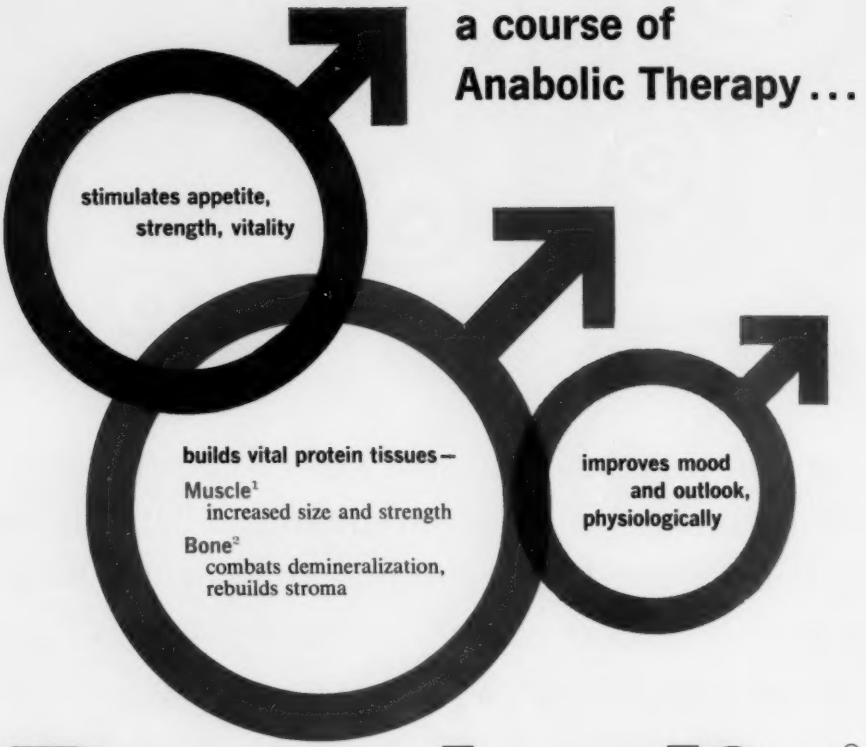

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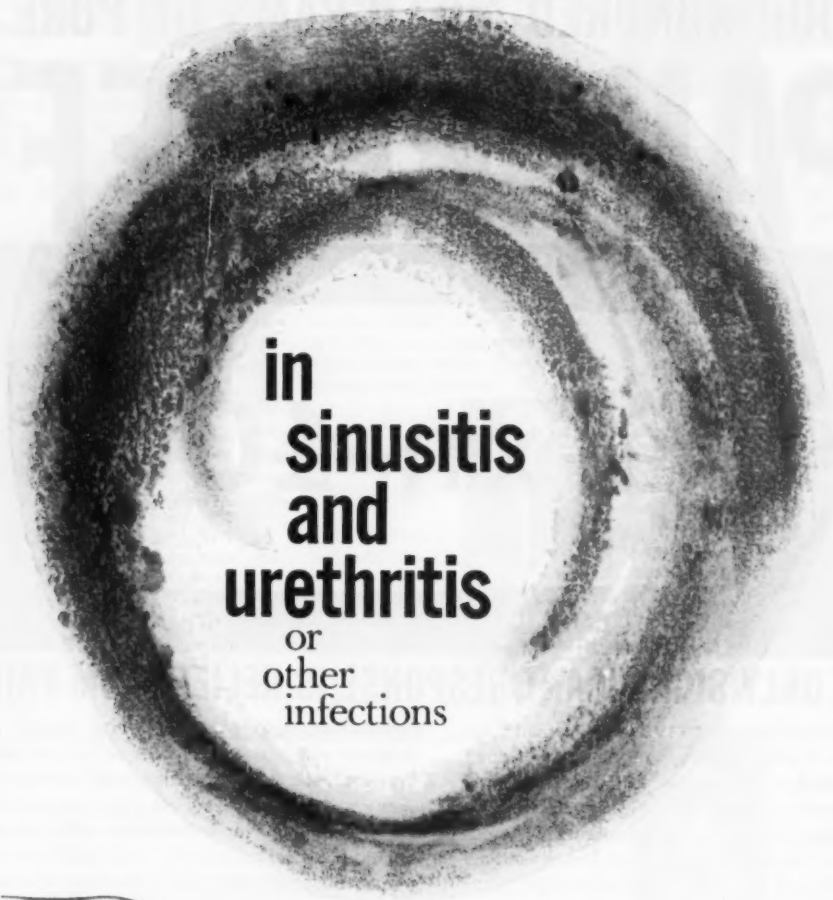

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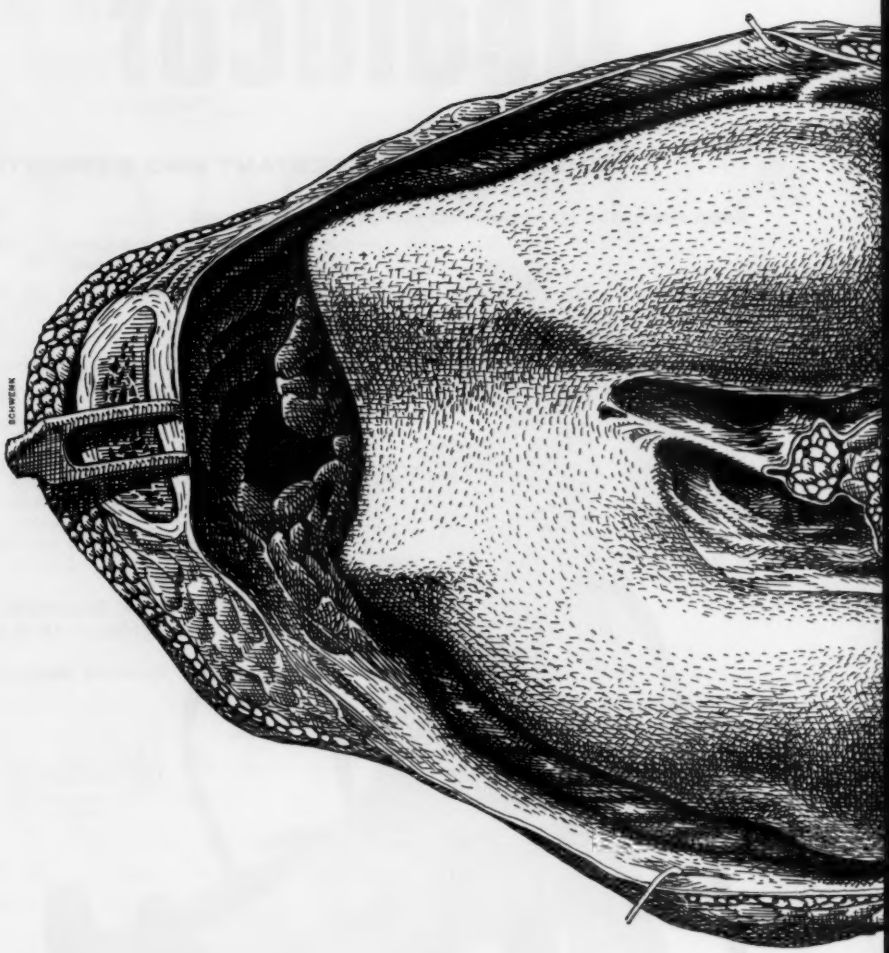

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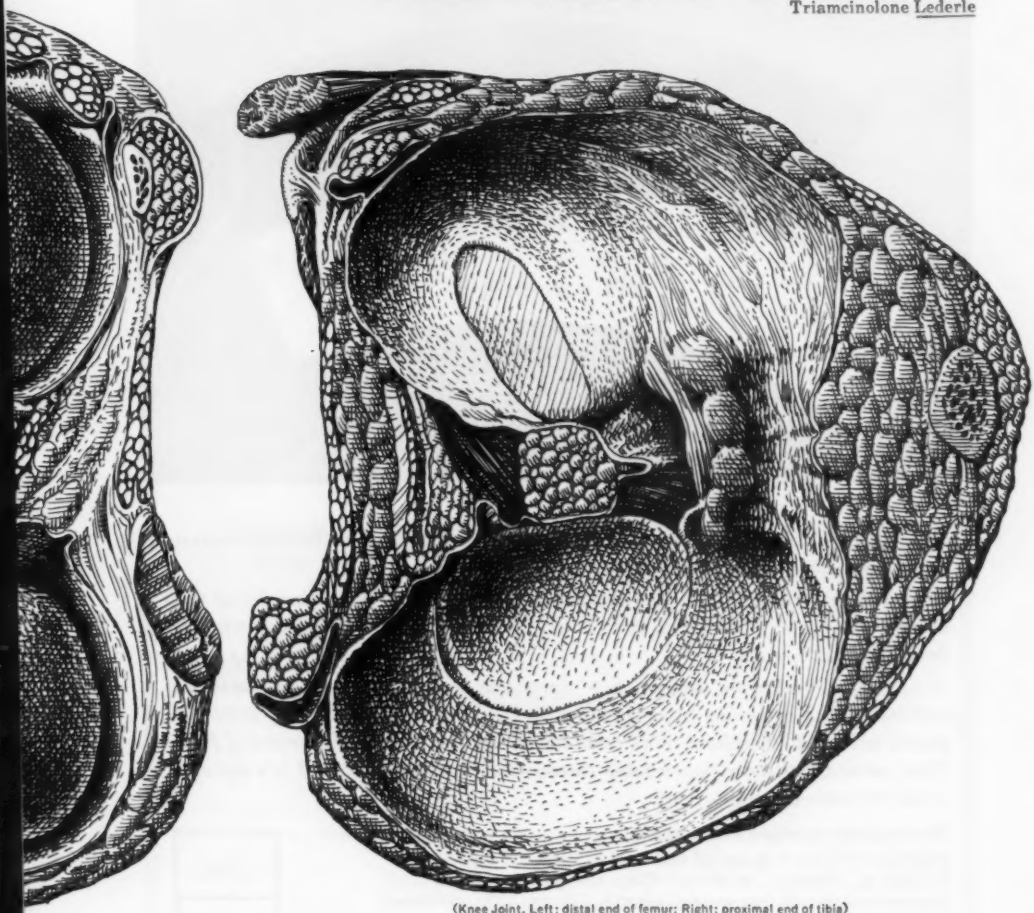

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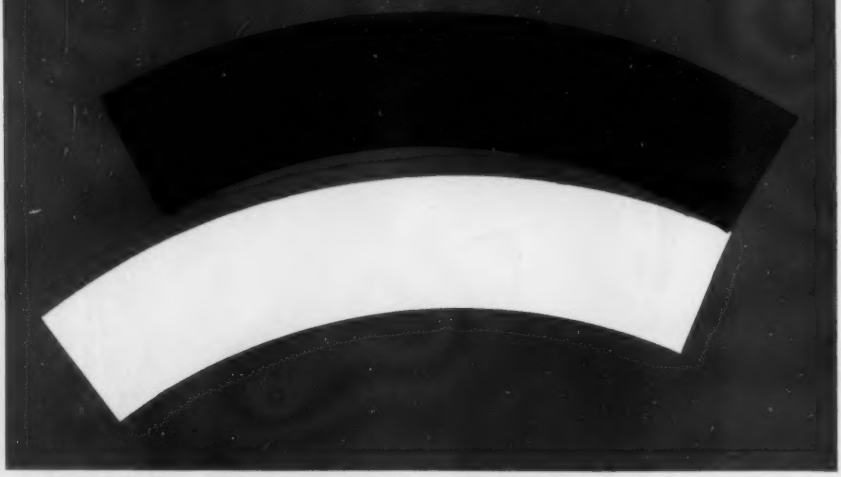

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AUTHORS ALONE ARE RESPONSIBLE FOR OPINIONS EXPRESSED IN THEIR CONTRIBUTIONS

ROBERT L. CRAIG, *Editor*

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THE NEW YORK ACADEMY
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NEW YORK PATHOLOGICAL SOCIETY

Presented at the Meeting on January 26, 1961, at The New York Academy of Medicine

MORBID ANATOMY BEFORE AND AFTER MORGAGNI*

The Twenty-Third Middleton Goldsmith Lecture

PAUL KLEMPERER

Consulting Pathologist, The Mount Sinai Hospital

IN 1761, Morgagni published his treatise,[1] "On the Seats and Causes of Diseases as investigated by Anatomy." Since then, Morgagni has frequently been called the "father of Pathologic Anatomy" and his monumental work its first textbook. Both claims are open to question. On the one hand, many records are available of necropsies performed for the explicit purpose of ascertaining the seats and causes of diseases which antedate the publication of Morgagni's masterwork;[2, 3] on the other hand, Schenck a Grafenberg's *Observationes*[4] and Bonetus' *Sepulchretum*,[5] likewise, had the same didactic aim of defining disease in terms of anatomic alteration. What, then, is the reason for celebrating the bicentennial anniversary of Morgagni's contribution to medicine? More than 200 years had preceded the publication of his book during

* From the Department of Pathology of The Mount Sinai Hospital, New York. Aided by a Grant of the Dr. Eli Moschcowitz Fund.

which time anatomic examination had played an increasingly commanding role in the investigation of disease, and 200 years have passed since it has come off the printing press. History has placed Morgagni in a period almost equidistant from the inception of pathologic anatomy and its present phase. His work can be appraised looking backwards as well as forward from his time. His contribution can be regarded as the culmination of a gradual evolution of morbid anatomy and also as the foundation of a new concept of pathology as it developed in the 19th and 20th centuries.

Belief in the utility of morbid anatomy for medicine can be traced to the Hippocratic book on *Ancient Medicine*[6] where it is stated, "I am further convinced that it is necessary to know what sufferings come to a man from powers and what from shapes. I mean, roughly, by power an extreme strength of humor, by shapes, the various forms to be found among the parts of the body". It seems as if, historically, the belief existed *a priori* among physicians that anatomic investigations contribute to a clearer understanding of the causes of diseases. But such explorations were precluded by a powerful taboo against contact with the dead body which was lifted for a short period only during the reign of the Ptolemaic kings. When, during the 13th century, restrictions were relaxed for the purpose of anatomical teaching, clinical autopsies were also soon performed. But the early reports did not clarify obscure clinical problems by the demonstration of relevant organ lesions. The anatomical findings were sometimes unequivocally described, but correlated with ill-defined clinical syndromes without empirical corroboration, while in other instances the reported anatomic alterations could not adequately account for the course of the disease. For example, in the case of Tornius,[7] symptoms of fever, discoloration of the face and dyspnea were interpreted according to Galen and Avicenna as evidence of obstruction of the liver and abdominal veins. The autopsy disclosed multiple ulcerations of the liver, most probably pylephlebitic liver abscesses in today's terminology, in addition to obliterating plugs in the portal and inferior caval veins. This satisfied Tornius to make the final comment: "So I was assured on seeing the chilic veins that there was an obstruction, as I had suspected." On the other hand, Benivieni[8] does not account for well-defined clinical symptoms in terms of unequivocal anatomical alterations, except in cases where such correlation is obvious. This unsophisticated attitude is illustrated in his description of an intes-

tinal obstruction by a callous mass, evidently a carcinoma. His comment is: "This, however, I had suspected even in her lifetime, seeing that she had struggled against something hard that pressed on her bowels." In subsequent years, many more observations were recorded in which the leading clinical symptoms were determined by mechanical factors disclosed at autopsy. Fernel[9] in 1567 summarized such situations in the following paragraph: "Similar to obstruction is constriction and narrowing of the intestine. This may be produced by the actions of things ingested, whether foods, as bad bryony, or astringent drenches, also by tumour of the mesentery or by the viscera pressing on the intestines and this is extremely common. It also happens from enterocele when the intestine comes down into the scrotum and is constricted by it as by a loop. Each of these ought to be perceptible of itself and not indirectly." Bonetus'[5] *Sepulchretum* is replete with autopsy records in which morbid symptoms affecting various regions of the human body are unequivocally correlated with anatomic alterations acting as mechanical impediments. All the great physicians of the two centuries preceding the publication of Morgagni's work opened the bodies of their deceased patients, anticipating to account for the clinical symptoms as a result of perceptible anatomic changes. It was a sort of common sense pathology which even those whose fundamental idea of the nature of health and disease was far from materialistic did not reject. Thus, van Helmont[10] refers to many necropsies which he performed on hydropic patients in order to ascertain whether the liver was affected or not. Even Sydenham,[11] who saw the possibility of progress in medicine only in exact bedside observation, did not altogether disapprove of autopsies but conceded their limited usefulness for the medical practitioner. Only John Locke[12] rejected anatomy as a tool of medical investigation. With the advance of rational physiology since Harvey, clinical symptoms could better be interpreted in terms of disturbance of organ functions and consequently more appropriately correlated with observations at the autopsy table. Thus, not only diagnostic medicine was enhanced but also new problems proposed for physiology. Edematous and cold extremities were correctly interpreted by Brunner[13] in his discussion of the autopsy of his father-in-law, Johann Jacob Wepfer, as the result of a failing greater circulation and not of a loss of innate heat. That cyanosis and dyspnea are due to stagnation of the pulmonary circulation was pointed out by Vieussuns and Albertini.[14, 15] That apoplexy is

caused by rupture of cerebral arteries was disclosed by Wepfer.[16] Sudden death due to occlusion of cardiac arteries was suggested by Bartholin.[17] Gangrene of the extremities was accounted for by ossification, and narrowing of the arteries by Evelyn and Cowper in 1702[18] and by Naish [19] in 1721. The association of polyuria with contraction of the kidneys was recognized by Wepfer[20] 150 years before Bright and Christison and this puzzling problem of renal pathology first exposed in terms of anatomic localization.[20a]

In 1679, Théophile Bonet assembled from the literature 3,000 cases in which clinical data had been reported with corresponding autopsy findings and complemented with explanatory remarks. Indeed, this collection shows the notable achievements of morbid anatomy over the past two centuries, but it also illustrates that its localizing principle had failed so far to account for a multitude of diseases. It could answer some of the problems of a crude mechanistic doctrine of health and disease as proposed by Descartes, but left unanswered the ultimate questions of the factors which regulate normal and abnormal life. For more than 2,000 years a speculative humoral pathology had satisfied the curiosity of the medical profession; the emerging modern basic sciences of physics and chemistry could easier be assimilated to this doctrine than aligned with an unsophisticated concept based on the as yet inadequate empiricism of morbid anatomy. Therefore, humoralism reinforced by iatromechanics and iatrochemistry could successfully compete with solidism proposed by morbid anatomic investigations. In fact, humoral speculations could be used for the explanation of anatomic organ alteration as evidenced by the writings of Malpighi[21] and Lancisi.[22] This was the intellectual climate of medical theory at the beginning of the 18th century when Morgagni entered the arena. The soundness of the principle of interpreting by anatomy the symptoms of diseases was established, but information was still fragmentary and not adequately collected and catalogued. Bedside and autopsy observation had still to be developed to a higher accuracy and validity of correlation critically examined. To assemble all the pertinent clinical and anatomic facts and to recognize their interrelations required a man of broadest experience and an exceptionally keen mind. To complement one's own observations with those accumulated over a period of 200 years in the literature of Europe called for a man of rare scholarship. And finally, it required the unshakable conviction that this work had to be done. Morgagni

brought all these qualifications to the task. He had been schooled by his teachers, Valsalva and Albertini, in the strict anatomical tradition of Malpighi, whose scientific grandson he proudly pronounced himself. It is generally maintained that Morgagni was primarily a morbid anatomist and his training and subsequent work in anatomy lend credence to this belief. But Jarcho,[23] in a penetrating study, challenges this opinion and shows from his writings that his interests were by no means strictly morphological. A perusal of the "Seats" reveals that Morgagni paid at least equal attention to the description of bedside symptoms as to autopsy observations of organ alteration. Morgagni's practical orientation directed him toward advancing clinical diagnosis, not as an end but as a means to the ultimate purpose of alleviation and cure of disease. This aim is well illustrated by his endeavor to discover pathognomonic features by persistent correlation of clinical symptoms with anatomical alterations. His attitude is revealed in many parts of his books and clearly expressed in his prefatorial letter to Johann Friedrich Schreiber.

He had at his disposal the material of the Hospital of St. Francesco in Padua, the records left to him by his teacher Valsalva and, last but not least, the observations of preceding generations. For nearly 60 years, he assembled data before he completed his monumental work. He had gained his reputation as a superb anatomist by his previous treatises, the *Animadversiones* and the *Epistolae Anatomicae*, which made him the undisputed leading anatomist of Europe. In 1708, he was elected a member of the Leopoldino Carolino Academy in Germany of which he became a deputy president in 1732; in the subsequent decades, all the national scientific societies of Europe selected him for inclusion in their ranks. In 1716, Boerhaave offered him without success the Chair of Anatomy at the University of Leyden, and Senac, in 1749, referred to him as the illustrious author of a forthcoming encyclopedia of anatomy. But anatomic investigations were not the ultimate aim for Morgagni, not even if pursued for elucidating the actual functions of organs; they were only means to the end of advancing the theory of medicine and of its practice. And so he wrote these books "concerned with the history of pathologists more than with anatomists", as he stated in his letter to Senac, prefatorial to the third book. But his vista of pathology is limited, though by intent. He was aware of those authors, who "affirmed that the causes of health as well as of most maladies are inaccessible to the senses, since they rest in hidden forms of invisible

particles, in their connections and movements and its forces which control these movements and connections". But he is not concerned with these hidden reasons "because it does not follow that the effects of these causes necessarily also escape our senses; for they affect perceptible parts and the abnormal alteration, which we discern in them, are the manifest internal causes of very many diseases". With this statement Morgagni unequivocally states the positivistic aim of morphologic investigation for the advance of medicine and refrains from hypothesis and ratiocination. He accepts only observation and description and his goal is a Natural History of Diseases, in the sense of Bacon, in which symptoms are correlated with anatomic alterations and these data reciprocally indexed. These indexes should serve, as he writes in the preface: "So that if any physician observe a singular or any other symptom in a patient and desire to know what internal injury is wont to correspond to that symptom; or if any anatomist find any particular morbid appearance in the dissection of a body and should wish to know what symptom has preceded an injury of this kind in other bodies; the physician, by inspecting the first of the indexes, the anatomist, by inspecting the second, will immediately find the observation which contains both (if both have been observed by us)."

Morgagni's fundamental objective was that of exact empiricism. He had the vision of a catalogue in which all the disease phenomena were critically collected and cross-indexed. His aims can be compared with those of Diderot, when he conceived his plan of an encyclopedia. He was aware of the magnitude of his project and invited the cooperation of all physicians and anatomists. (Letter to Frederick Meckel.) He foresaw that future generations would still be engaged in the task of providing the medical profession with a complete register of integrated clinical and anatomical data. He tried to caution future investigators of the pitfalls of anatomic observations and pointed to organ alterations occurring in the moribund patient and even after death. Such changes had often been misinterpreted in the past, as, for instance, postmortem coagula had been considered polypi of the heart. He cautioned that a correlation between anatomical findings and clinical symptoms must be validated by an adequate number of observations, the statistical principle already stressed by Francis Glisson[24] 100 years before. He emphasized the importance of listing age, sex, marital status, occupation and climatic conditions affecting the patient, and did not neglect to point to previous

diseases and hereditary factors which should be looked for. Thus, he emerges from his writings as the great teacher, a vocation which was most precious to his heart, a sentiment he unequivocally expressed in his letters to Senac and Schreiber. The didactic orientation transpires throughout his five books and is expressly stated in the prefatory pages. The dynamism of teaching elicits, as a necessary corollary, a desire for more learning. It is the combination of these two forces in Morgagni which explains how morbid anatomy, as sponsored by him, did not become a mere branch or tool of medicine but its discipline, and that it could grow harmoniously beyond the peak it had reached with him.

Morgagni's books were received by the medical world with the greatest respect. *The Göttingische Gelehrte Anzeigen* of July 25th, 1763, wrote that it would be impossible to abstract his "important and for all true physicians indispensable work". Haller[25] referred to them as most significant and important and praised Morgagni for having been an outstanding anatomist in his youth and for having reached even higher eminence in his advanced years by his most important contribution to the practice of medicine and morbid anatomy. The books were translated into English in 1769, into German in 1774. They were followed in due course by similar collections of clinical-anatomic correlations, such as those of Lieutaud[26] and of Sandifort.[27]

It had been stressed by Morgagni that a full comprehension of disease demanded its localization in order to define it. An awareness of this postulate emerges in the regretful remark of Heberden[28] in his first publication on angina pectoris when he writes of his inability to perform an autopsy on any one of his patients. This example well illustrates that Morgagni's contemporaries were cognizant of the value of post-mortem examination, but not convinced of its indispensability for a deeper understanding of disease. However, the nature of this "disorder of the breast" began to be clarified only when Jenner and Parry[29] established its correlation with coronary artery ossification in 1799. It is at the turn of the century that the impact of Morgagni's thesis gained momentum. It does not detract from his glory if it is reiterated here that the idea of clinical-anatomical correlation did not originate with him, but he advanced it with his authority and his monumental contribution. One must not fail to mention that Boerhaave, in Leyden, had already made obligatory post-mortem examinations on the patients whom he had presented to his students in his clinical demonstrations.

It was under the influence of his disciples, Van Swieten and De Haen, that the same practice was introduced in the government hospitals in Vienna in the middle of the 18th century, and it was in Vienna where a new idea was born which was to vitalize the principle of congruence of observations in the living and in the dead which Morgagni had advocated so persuasively and codified at the end of his life. Leopold Auenbrugger's slim *Inventum Novum*[30] appeared in the same year as Morgagni's voluminous work. Here the novel idea was first proposed to make morbid lesions of the chest perceptible by percussion. Obviously, this brilliant discovery could be fully utilized only if the anatomic rationale had already taken firm roots in medicine. It had not, and it required nearly 50 years until Auenbrugger's genius found full recognition, thanks to the discernment and generosity of Corvisart. With this ingenious clinical technique new diagnostic symptoms were added to the conventional criteria of medical examination, aiding the ultimate aim of an anatomic diagnosis of organ alterations in the living. That this was the aim was succinctly expressed by Corvisart[31] in the preface to his essay on cardiac diseases, in which he recommended the preparation of "a book analogous to that of Morgagni but the converse of it"; it would be titled, "On the Seats and Causes of Diseases, Investigated by Diagnostic Signs and Confirmed by Autopsy". "But," he added, "for such a work we would need at least a second Morgagni." Corvisart's prophecy has come true. It was advanced by Laennec's discovery of auscultation, and was carried to unexpected heights by roentgenology and the diverse modern methods of biopsy in the literal meaning of the word. It still shows its value and vitality in the clinical-pathological conferences of today. The history of medicine of the first half of the 19th century has proven Corvisart right. But it required more than a book to consolidate the new rational medicine based on morbid anatomy. It developed all over Europe but reached its height in France under the inspiration of Pinel, Bichat and Corvisart; in England, of John Hunter. The achievements of these schools of medicine with primary anatomic orientation within the span of the first decades of the century cannot be given in detail. But reference should be made to the discovery of the characteristic intestinal lesions in the obscure putrid, ataxic or typhoid fever by Petit and Serre in 1813,[32] because it brought into sharp focus the basic inadequacy of single-minded clinical-anatomic correlation. More than 50 years before, Senac and Morgagni

had remarked on the absence of obvious anatomic alterations in the group of malignant fevers to account for the leading symptoms (Morgagni's letter to Senac[33]). Now the new observations had disclosed unequivocal intestinal lesions; but how could they be correlated with the equally striking and variegated morbid phenomena during the life of the patients? It is true that Petit and Serre had recognized that the initial symptoms of the malady pointed to an affection of the intestines, an observation agreed upon by all subsequent observers; but how could all the other conspicuous symptoms, especially the severe cerebral affection and the prostration be explained? This uncertainty is revealed by the remark of Cruveilhier[34] who was familiar with the disease both clinically and anatomically. Referring to the entero-mesenteric fever of Petit and Serre, he raises the question whether the organic alterations reflect the principal disease, or a complication, or whether they are an effect of the fever. He even questions the specificity of the intestinal lesions which he believes to occur in several other maladies, among which he mentions mainly pulmonary phthisis. This, of course, showed only diagnostic inadequacy, which was soon corrected, as can be recognized in Richard Bright's classical plates[35] which clearly illustrate the differences between tuberculosis and typhoid ulcerations. Bretonneau[36] in 1829 unequivocally maintained that the disease, which he called DOTHINÉNTERIE, is accompanied by intestinal eruption but not caused by it, "because one cannot, without grave error, attribute the morbid phenomena characteristic of it to an intestinal inflammation". These were serious challenges of the universal validity of Morgagni's fundamental assumption that anatomical alterations were the proximate causes of diseases. They questioned the wisdom of his attitude of refraining from concern with the hidden causes of disease. They indicated that morbid anatomy could not remain satisfied with merely demonstrating a parallelism between clinical and morphologic phenomena of disease, but that it had to aim at a comprehension of the nature of the anatomic lesions. If pathology is that aspect of medicine which is concerned with the cause of disease and the mechanisms by which it is provoked, then, if morbid anatomy is to be auxiliary to pathology, it must abandon its static taxonomic position and has to inquire into the reasons for structural aberration; in other words, it has to develop into anatomic pathology. The findings of Petit and Serre and of their successors offered a key which opened a new approach for a better comprehension of dis-

ease through morbid anatomy. Their exact observations had disclosed that the intestinal lesions of typhoid varied with the duration of the illness. This indicated that the structural alterations were dependent on a biological evolution and therefore had to be regarded as the product of a morbid process. This concept vitalized the interpretation of the static structural anomaly and prevented morbid anatomy from becoming a mere appendix of diagnostic medicine. It oriented Bayle[37] and Laennec[38] in their investigations of pulmonary tuberculosis; it led Abercrombie[39] and Rostan[40] to recognize encephalomalacia as the result of vascular occlusion; it transpired in Bright's discussion of his new disease. The importance was fully recognized by Lobstein, but it became the lodestar for Rokitansky and Virchow and it still dominates the philosophy of our discipline today. While a chronicle of pathologic anatomic discoveries seems to indicate that the concept of the morbid process was advanced in the 19th century only, it has to be affirmed that it can already be recognized in the lectures on surgery of John Hunter[41] and his works which were published after his death. He was led to the principle by his observations as a surgeon and guided by it in his studies and experiments on inflammation. Matthew Baillie,[42] his nephew and disciple, grasped the importance of the pathogenetic principle for the advance of morbid anatomy when he wrote in the preface to his textbook that "the object of this work is, to explain the changes of structure arising from morbid actions". But he realized that the observational material was still inadequate because he continued, "it is very much to be regretted that the knowledge of structure does not certainly lead to the knowledge of morbid actions although the one is the effect of the other". He was aware of the difficulty of gaining knowledge, "because", he said, "morbid actions are going on in the minute parts of an animal body excluded from observation". This assertion sounds like that of John Locke,[12] who had maintained about 100 years before that "nature performs her operations in the body by parts so minute and insensible that I think nobody will ever hope or pretend even by the assistance of glasses to come to a sight of them". Yet, Baillie did not share Locke's pessimism because he ended his considerations with the affirmation that, "examination of morbid structure seems to me to be one of the most probable means of throwing light on it". And the development of the next 50 years proved him right.

But the historian has to caution himself not to attribute conceptual

advances in medicine to selected observations or to the genius of individual investigators. The dynamism which began to pervade the studies of morbid anatomists in the first decades of the 19th century originated in the conscious efforts of physiology to analyze experimentally the actions which take place within the parts of the body. Not that the idea of a function of organs was alien to preceding generations of physicians. Galen had written books on the subject, and the great anatomists of the 16th and 17th centuries had paid equal attention to structure and function. To quote only Glisson[43] among them: "Nobody is interested in the manual dissection of cadavers if it does not bring light to the comprehension of the living." But the well-spring of action was not observed but left to speculation, be it that of an Archaeus, an Anima, or of the less mystical but not better comprehended forces invoked by iatromechanics and iatrochemists. The first determined effort was made by Albrecht von Haller to investigate the actions of parts of the body in reference to two phenomena which he observed by experiments. These were the elicitation of pain and of contraction. In his essay[44] on the "sensible and irritable parts of the human body" he concluded that the vital phenomena are determined by a particular organization of the respective tissues, reacting to stimuli, an idea which was fully developed by Virchow in his cellular pathology. I shall not enter into a discussion of the far-reaching and erroneous conclusions which were drawn from Haller's strictly physiologic observations as regards an explanation of the nature of disease, such as, the neuristic theory of Cullen and particularly John Brown's irritability doctrine. But I should like to point to the connection between Haller's fundamental observation of the localization of vital phenomena within well defined anatomic structures and the ideas of Bichat.

The assumption that the function of organs depends on a special vital force and not on mechanical factors, an idea contrary to that of Boerhaave, was first expressed by Théophile Bordeu[45] of Montpellier in the same year in which Haller published his essay. Bordeu, 16 years later,[46] was again the first who pointed to the cellular tissue, today's connective tissue, as the seat of many diseases. Both suppositions are combined in Bichat's doctrine. It is obviously impossible to give in this address an abstract of Bichat's observations which culminated in his General Anatomy, his essay on the membranes and on life and death. But it might be permitted to quote two sentences which succinctly sum-

marize his beliefs.[47] They could be duplicated by many more. "I believe that the more one will observe diseases and open the cadavers the more one will be convinced of the necessity of considering local diseases not from the aspect of the complex organs but from that of the individual tissues." And his physiological concept he expressed with the following sentence: "To apply the physical sciences to physiology means to explain the phenomena of living with the laws of dead bodies. Leave affinity to Chemistry, to Physics its elasticity and gravity, to physiology pertains only sensibility and contractility." Bichat's definition of tissues, and the idea of localization of morbid processes in them and not in complex organs, was generally accepted as evidenced by Hodgkin's lectures on the morbid anatomy of the serous and mucous membranes.[48] How far Bichat's cumbersome method of tissue investigation influenced the observations of pathologic anatomy is not easily ascertained, because the microscope was soon introduced for the study of finer details.* His importance for the advance of the discipline was undoubtedly due to the enthusiasm which he kindled among those with whom he came in contact. Dupuytren, Laennec and Bayle were his direct pupils, and through these, new future generations were instructed in pathologic anatomy, among them Cruveilhier and Louis in France, Hodgkin and Carswell in England and Gerhard in this country. Bichat's doctrine of life and his rejection of physical or chemical explanation of phenomena of the living organisms soon met energetic opposition. It grew when the advances of organic chemistry showed that the assumption of a difference between organic and inorganic matter was not tenable. The idea of vital tissue qualities and forces is no more acceptable today, but it played an important role in the development of biology, because it encouraged the incessant efforts of the exact sciences to refute it and to substitute physico-chemical laws for the ill-defined actions of a hypothetical force.

Notwithstanding these cogent objections, both doctrines of Bichat equally contributed to the evolution of pathologic anatomy in the subsequent decades. His morphologic proposition of localizing the anatomic alterations in the tissues instead of the complex organs was by itself a refinement only of Morgagni's original thesis. Linked, however, with the postulation of a force, regulating the life of the tissues, the idea was

* His immediate pupils did not engage in a study of the tissues but remained interested in the lesions of the whole organs and developed pathologic anatomy in such a manner that it became known under the name "organicism".

introduced into the study of structure of causal determinism, an idea from which Morgagni had kept aloof intentionally. To the assertion that the causes of health as well as of most maladies are inaccessible to the senses, he had replied with a skeptical "even if true" in his letter to Senac. Forty years later, the question could no longer be sidestepped, if morbid anatomy was to contribute to general pathology, the fundamental theory of medicine. It was, however, scientific search for the internal causes of tissue changes which was to be launched only in the years to come; neither postulation nor speculation could bring about the transformation of Morgagni's unsophisticated concept. Interestingly, most morbid anatomists of the first third of the 19th Century were not aware of the crisis in which their discipline would find itself in the not too distant future. In fact, that period witnessed some of the most important contributions to medicine yet achieved by the classical correlative principle of Morgagni, such as Laennec's monumental work on *Diseases of the Chest*,[38] the discoveries of Bright[35] and Hodgkin,[49] in addition to those already mentioned previously. Medicine in France, England and in Germany under Lucas Schoenlein following the decline of NATURPHILOSOPHIE was conducted mainly along diagnostic lines with morbid anatomy as the sole guide. It is obvious that such an orientation was not disposed to advance the ultimate aim of curative medicine which could only be established upon a sound scientific theory of general pathology.

Karl von Rokitansky and Rudolf Virchow are commonly regarded as the originators of a new pathologic anatomy. But again, history reminds us that new concepts in medicine do not arise *de novo* in the minds of single individuals; they are the results of a slow evolution which is only catalyzed by the clarity and perseverance of the chosen few. The impasse in which morbid anatomy found itself in the thirties of the 19th century was recognized by Lobstein in France and Johannes Mueller in Germany, and we can trace to their writings the immediate stimulus for modern anatomic pathology. In the preface to his textbook,[50] published between 1829 and 1833, Lobstein, the worthy descendant of Bichat, gave an outline for the organization of pathologic anatomy. Of his points I shall select a few because they represent a blueprint for the work of the future. It is founded upon exact description of the anatomic lesions according to position, shape, volume and internal structure of the affected organ and its relation to other anatomic systems with which it is connected in more or less sympathy, in

plain language, concomitant lesions of other organs. Under the term, "pathogenesis", first used by him in pathologic anatomy, Lobstein embraces the investigation of all questions regarding origin, formation and evolution of the organ disease. The final but not less important objective of pathologic anatomy is to correlate the organic alteration with the morbid phenomena observed during life. This is, of course, the classical precept of Morgagni. But Lobstein demanded a more penetrating analysis of the phenomena in order to determine to what degree they are dependent on the anatomic lesions. Such an inquiry should aim at a distinction of the original symptoms which pertain to the immediate affection of the vital force from those which are direct consequences of the manifest alterations of the tissues. Lobstein's principles of pathologic anatomic investigations have been faithfully followed by Rokitansky who in his autobiography acknowledged his indebtedness to him. If Lobstein said that "the physician does not want to concern himself with the dead organ but with that which lives and acts", Rokitansky carried out this objective because he taught, as Klebs[51] expressed it, "to think anatomically at the bedside and to weave at the autopsy table the individual phases of the morbid process into the pattern of the clinical progress". This was the program of which Rokitansky spoke[52] to his students at his first lecture as full professor and to which he turned 30 years later in his last lecture[53] when he said: "I have pursued Pathologic Anatomy as a science aiming at fertilizing clinical Medicine." But Lobstein's influence went beyond stimulating Rokitansky's endeavor of promoting conventional morbid anatomy. The recommended separation of the aims of correlation was an equally important clue for Rokitansky's interpretation of autopsy findings. The symptoms pertaining to affection of vital forces could not be expected to correspond to local changes of organs, but rather to those of the all-pervasive humors of the body, particularly the blood. It seems to me that his crasis doctrine derived from that assumption. It is true that this speculation collapsed under the harsh critique of Virchow. But Rokitansky had realized that investigations of the whole blood could not be adequately carried out with the methods of morphology but demanded profound chemical research. And so the ill-fated "Krasis Doctrine" gave birth to a scientific exploration of the altered constitution of the blood, and Rokitansky conceived of a discipline devoted to the chemical aspects of pathologic inquiry, as he affirmed in his first lecture. This inspiration came to its

fulfillment in 1862 when the new Institute of Pathologic Anatomy and Pathologic Chemistry was opened in Vienna.

Historians have always been aware of the decisive influence Johannes Mueller had on the life work of Rudolf Virchow, and he has acknowledged it in his memorial address of this great scientist. But it might not be amiss to hear what Mueller had to say about the crisis in pathologic anatomy and how he proposed to meet it. In 1834, he wrote,[54] "Pathologic Anatomy continues to offer us a large amount of observations but their comprehension advances all too slowly. Among the obstacles of a further evolution one has to blame principally the unscientific casuistic trend with which it is pursued. It is carried out only for correction of diagnosis and not for the aim of advancing Pathology." And he points to the method by which this could be accomplished. "If anything should come out of the study of Pathologic Anatomy, physicians must not limit themselves to autopsy reports; the structure of the altered tissues must be investigated which requires adequate anatomic and physiologic experience". Johannes Mueller started this program with his study, "On the Finer Structure of the Forms of Neoplasms", but it was Virchow who completed it with his cellular pathology. Virchow is commonly regarded as the father of cellular pathology but not as the creator of the cell theory. This is correct, and it should be added that Theodore Schwann had already indicated that his cellular theory of the formation of normal tissues applied also to a great variety of pathologic organizations. Neither should it be ignored that Karl Remak preceded Virchow in the recognition that Schwann's original idea of cell formation from a formless blastema was not tenable and that he, prior to Virchow's early pronouncements of cellular pathology, published an article[55] in which he demonstrated that the principle of successive cell generation applies also to neoplasms. It might seem, therefore, that Arnold Rich[56] in 1926 was justified when he stated that "it required not much imagination to apply the microscope to the examination of morbid products". But Virchow's histopathology is not a mere refinement of Morgagni's thesis to recognize the perceptible organ changes, an advance of Morgagni's anatomy, thanks to technological progress. What we owe him is a new scientific approch to the comprehension of the nature of disease through analysis of structure. Through him the microscope became a reformatory instrument, not a mere diagnostic tool; in short, he is the creator of anatomic pathology, the morphologic discipline

which inquires not so much into the cause of disease as into the mechanisms by which it is provoked. I believe we can accept this restricted definition for our times. But in the years of Virchow's greatest triumph cellular pathology was acclaimed as the essence of pathology in general. This claim led to a crisis which came into the open at a meeting of the German Naturalists and Physicians in 1877. In an address entitled, "The Transformation of Medical Concepts in the Last Three Decades", Edwin Klebs,[51] a former assistant of Virchow, spoke respectfully but critically about the inadequacy of cellular pathology as a general theory of diseases. It was the rejection by Virchow of the recent achievements of bacteriology which prompted Klebs to refer to cellular pathology as "a theory which does not provide clarification of the causal conditions of diseases". The judgment of history has endorsed Klebs. But it might be informative to dwell on the question, how was it possible that the great Virchow should have been so blind as not to recognize the transcendental significance of the discoveries of Pasteur and Koch? A statement of Klebs might help to bring the issue into focus. I refer to the sentence in which he speaks of an "extreme doctrine which regards all morbid processes as purely internal events and completely neglects the importance of external factors which provoke the diseases". This doctrine was the result of Virchow's deliberate preoccupation with the comprehension of vital phenomena by concentrating upon their manifestations within the cells of the body. He was fully aware that an ultimate theory of disease must derive from coordinated investigations at the bedside and at the autopsy table and must include an inquiry into the morbific factors tested by experiment. This was his original program which he had outlined in 1845,[57] to which he adhered to the end of his life, and the execution of which he tried to advance by his research and by numerous inspiring lead articles in his *Archiv* and other publications. It was this great vision of universality which made him the leader of German Medicine and for which he was recognized all over the world. But for his own contribution in this grand scheme of endeavor he selected investigations of cell structure, in order to comprehend the phenomena of life. Truly, not structure in a narrow morphologic sense; for that we have him as a witness when he maintained that the alteration of the cell which he visualized in his mind need not be anatomic: "Can it not be chemical?" he asked.[58] Nine years later,* he

* At a meeting in Stettin in 1863.

gave a blueprint of his aims for analytical pathology: "When I called attention to the cell I intended to urge the individual investigators to identify precisely the events within the cells, what takes place within these smallest elementary organisms; and it was self-evident that this precise identification could not be anything else than to find the physical and chemical foundation upon which rest the vital phenomena."[59] This sounds like an up-to-date manifesto which should satisfy the most modern cell biologist, and it may hearten the anatomic pathologist daunted by the spectacular advances of today's biochemists and biophysicists. We must be grateful to Klebs for his criticism of cellular pathology, because it gave Virchow the opportunity[60] of clarifying his position and that of anatomic pathology. Just like Morgagni, who refrained from searching out the hidden causes of diseases and was satisfied with investigating their perceptible effects upon the organs of the body, Virchow did not concentrate upon identification of external factors which provoke the morbid state. But he was fully aware of their significance and expressed it repeatedly in subsequent articles, for instance, when he "calls attention to the fact that morphology represents only one aspect of biology and that beyond the confines of morphology there is a large area of mechanical and chemical events whose investigations require methods other than those morphology can supply". This statement reflects a balanced estimate of the potential of structural research. That Virchow did not unreservedly accept the microbic theory of infectious diseases can be accounted for by the extravagant and not always fully proven claims which some of the early enthusiastic followers had made, to whom he refers in his answer to Klebs. Another reason was his apprehension that the concept of disease as a living entity, held by German NATURPHILOSOPHIE only a generation before, could be revitalized by speculative minds. He had fought these erroneous ontological notions in the beginning of his career and was sensitized to them. He did not realize that these ghosts had been banned forever.

Klebs' courageous but restrained critique of cellular pathology was matched by Virchow's conciliatory response. When Klebs expressed the hope "that an agreement could be reached in the interest of the problems which cannot be solved by a single person", Virchow referred to misunderstandings which can be clarified, and disclaimed "the pretense that cellular pathology was meant to be a general Pathology".

The dignified controversy cleared the air and opened the road for auspicious cooperation of all sincere students of disease. The following generations of pathologic anatomists joined the ranks of those who had revolted against an all too narrow limitation of pathologic research and contributed to the rapid development of bacteriology and immunology, without abandoning their prime interest in anatomic pathology.* It became evident that exclusiveness of purpose was harmful for the advance toward the common goal, general pathology, as the integrated comprehension of all the factors responsible for the morbid state. The ever-increasing scope of experiences in this endeavor is determined by an ever-increasing variety of methodology. We are sometimes losing sight of the unifying aim. Accelerated specialization and petty jealousies between the groups harm the harmonious development of sound teaching and research and endanger the whole structure of medical education. Respect for the common past will counteract these harmful influences which otherwise might threaten the vitality of Pathology in its universal meaning as that aspect of Medicine which is concerned with the cause of disease and the mechanisms by which it is provoked.

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TREATMENT OF ANEURYSMS OF THE ANTERIOR COMMUNICATING (ACC) ARTERY*

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THE diagnosis of a ruptured aneurysm of the anterior communicating (ACC) artery of the circle of Willis is often difficult, because the first evidence of its presence is usually an acute subarachnoid hemorrhage without any localizing neurological signs.[1] Consequently, this condition is often overlooked until too late, because intracranial hemorrhage of this sort, especially in a hypertensive patient, may simply be attributed to a vascular accident.

However, now that prompt bilateral cerebral angiography has proved such a safe and effective diagnostic procedure, fewer of these dangerous lesions are being overlooked.

A recent review of good risk patients with such lesions has shown that, without surgical treatment of their aneurysm, close to 75 per cent die of a recurrent hemorrhage.[2] Even though induced hypotension is used in addition to bed rest and sedation, the mortality from further bleeding episodes is 33 per cent,[3] although it can be less than this if the same type of patient and lesion is operated upon.

While carotid artery ligation or clamping in the neck can be effective in preventing further hemorrhages, it may also be ineffective, and can have an associated mortality of approximately 20 per cent[4] and a morbidity, manifested by such complications as permanent hemiplegia or aphasia, of close to 18 per cent.[5] For these reasons the therapeutic procedure of choice would seem to be direct treatment of the aneurysm intracranially. In this respect, however, several important considerations must be weighed, such as the selection of patients for surgery, the timing of all operations, and the type of surgical approach.

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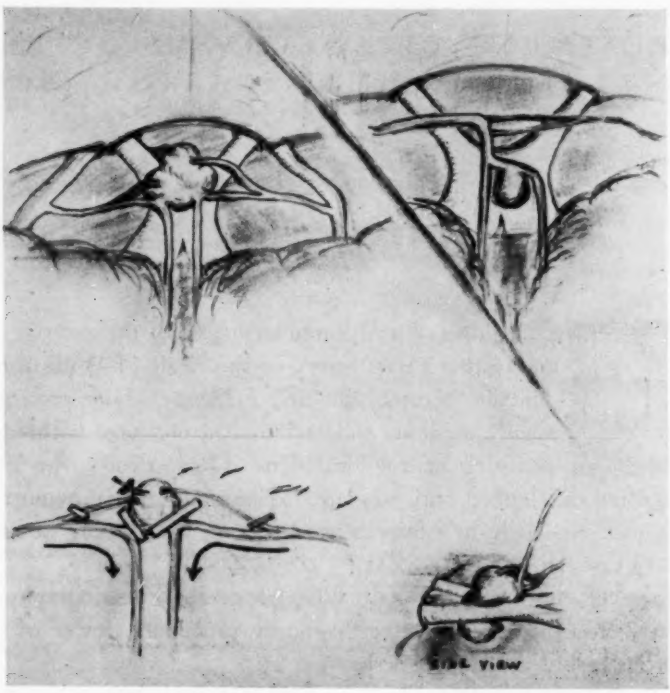

Figure 1. Difficult type of aneurysm of the anterior communicating (ACC) artery, above and straddling the optic chiasm.

Lower left: shows aneurysm clipped with preserved flow through both anterior cerebral (AC) arteries.

A recent review of more than 200 cases of ruptured ACC aneurysm treated by intracranial surgery by 20 capable neurosurgeons indicates that the age of the patient and the presence of vascular hypertension are not highly significant factors, although an age of over 50 years and documented hypertension of over 150/100 tend to increase postoperative morbidity and mortality rates. If the patient is alert rather than lethargic his chances are also somewhat better for a happy outcome following surgery. Comatose patients generally all die without surgery, whereas "salvage" surgery has saved the lives of a few such cases.

Experience, together with data from this recent survey, has shown that the surgical mortality rate is higher if operation is done within the

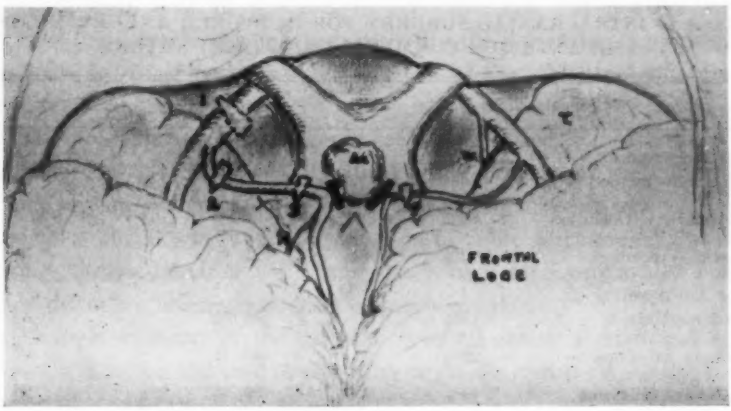

Figure 2. Shows aneurysm of the anterior communicating (ACC) artery permanently clipped. Dotted lines show position of temporary clip on: (1) left internal carotid artery until placement at (2) on left anterior cerebral artery proximally and then replaced at (3) closer to aneurysm at (4) temporary clip on right anterior cerebral artery. (No clip shown on right internal carotid.)

T = temporal lobe. P. C. = posterior communicating artery.

first 6 days after a subarachnoid hemorrhage, and is appreciably lower if operation is done from the 7th to the 10th day. Moreover, a few cases in excellent condition have died of a sudden recurrent hemorrhage because operation was delayed beyond the 10th day. For these reasons the optimal time for intracranial surgery on this type of aneurysm would seem to be between the 6th and 10th day after the presenting episode of subarachnoid hemorrhage. Such patients will presumably then be in better condition with respect to their intracranial circulatory status, and yet will not run any great risk of dying before surgical intervention can be offered. While it is true that the longer surgery is postponed the less are the risks of a poor result, lives may be lost by too great a delay.

As to the type of surgery, the recent survey of over 200 cases of ruptured ACC aneurysms treated by intracranial surgery shows the following mortality rates for favorable risk patients: Clip occlusion of the aneurysm, 16.4 per cent; proximal occlusion of one anterior cerebral (AC) artery only, 20 per cent; muscle wrapping of the aneurysm sac, 21.7 per cent; multiple clipping of anterior cerebral vessels, 40 per cent;

TABLE I—INTRACRANIAL SURGERY FOR RUPTURED ANEURYSMS OF THE ANTERIOR COMMUNICATING (ACC) ARTERY

Procedure	*Morbidity*	*Mortality*	*Total*
Clip Aneurysms T.C. clip method	20%	6.5%	26.5%
Proximal AC Occlusion	9%	20 %	29 %
Muscle Wrapping	13%	21 %	34 %
Clip Aneurysm All methods	19%	16 %	35 %
Multiple AC Clips	22%	40 %	62 %
Multiple Aneurysms	16%	50 %	66 %

multiple aneurysms, 50 per cent. Proximal AC occlusion and muscle wrapping of the aneurysm may not prevent subsequent fatalities due to recurrent hemorrhage. Clipping the aneurysm therefore seems preferable, especially as the mortality rate has now been reduced (for favorable risk patients) to 6.5 per cent, provided a bifrontal craniotomy flap is used to facilitate exposure, and temporary clips are applied to *both* anterior cerebral arteries to prevent premature rupture of the aneurysm at operation until it is clipped. Hypothermia and intravenous urea have helped reduce the surgical mortality for noncomatose patients, mostly operated upon within 6 to 14 days after hemorrhage, to 6.5 per cent.[1] Morbidity and mortality figures for the various forms of treatment of anterior communicating (ACC) artery aneurysms are given in Table I.

DISCUSSION

The figures reported herein are quite similar to those cited by McKissock, Paine and Walsh,[4] with respect to both unoperated and operated patients with this type of lesion as to mortality, and also as to the incidence of recurrent hemorrhages. Fisher,[6] moreover, has also referred to the peak incidence of recurrent hemorrhage in unoperated patients as occurring in the second week after their presenting episode of subarachnoid hemorrhage. Therefore, if surgery is to be undertaken

it would seem wise to proceed, in favorable risk but not comatose patients, between the 6th and 10th day after the presenting hemorrhage, especially for those patients under 60 years of age who are not severely hypertensive.

The procedure of choice would seem to be direct clip occlusion of the aneurysm.[1] If this cannot be done safely because of the condition of the patient or a brittle, arteriosclerotic aneurysmal sac, the sac may then be wrapped with a muscle stamp to promote surrounding fibrosis, or one anterior cerebral (AC) artery may be ligated proximally (provided the other, although smaller, is functioning).

Multiple clipping of the anterior cerebral artery system had best be avoided, as this can lead to crippling or fatal circulatory insufficiency due to serious cerebral infarction.

If more than one aneurysm is present the case should be managed either without surgery or by treating both aneurysms intracranially, preferably at the same operative procedure. Otherwise the second aneurysm (usually arising from the internal carotid or posterior communicating artery) may rupture fatally, as indicated by the percentage of poor results listed in Table I for such cases, unless both aneurysms are properly treated. Every effort should be made, of course, to determine which aneurysm has bled by searching for angiographic evidence of the local cerebral vasospasm that is usually present near a recently ruptured aneurysm.[7]

Additional data now being collected will undoubtedly clarify many of these points still farther.

Conclusions

1. Subarachnoid hemorrhage without localizing neurological symptoms or signs is characteristic of rupture of an aneurysm of the anterior communicating (ACC) artery.

2. Prompt cerebral angiography, bilaterally, is advisable for such patients.

3. Ruptured ACC aneurysms, if not treated surgically, sooner or later are apt to bleed again, usually fatally.

4. Surgical intervention, therefore, seems the procedure of choice for treating such aneurysms. While various techniques are discussed,

one of the most satisfactory methods is direct clip occlusion of the aneurysm, preferably with the aid of temporary clips, under hypothermia and after the administration of intravenous urea.

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IATROGENICALLY INDUCED LIVER DISEASE

*Transcription of a Panel Meeting**

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MODERATOR KLATSKIN: The problem of iatrogenically induced liver disease is a matter of concern to all physicians, whatever their specialty; hence, it is an appropriate subject for a meeting of this type. The physician may inadvertently produce liver injury in a number of ways. Of these, the two most important are the accidental transmission of the hepatitis virus and the use of certain drugs.

Although the incidence of iatrogenically induced viral hepatitis has declined since physicians have become aware of the dangers involved in the use of improperly sterilized instruments, the threat of infection following transfusion of whole blood or its products remains as great as ever.

With respect to drug-induced hepatitis, the incidence appears to be on the increase and, indeed, appears to parallel the ever increasing number of new drugs being introduced in therapy.

By way of introduction, I would like to make a few comments about drug-induced liver injury. Unfortunately, the term hepatotoxin is often applied to all drugs that give rise to liver injury. This is an unfortunate practice since it encourages the misconception that all drugs injure the liver in the same way. Current evidence suggests that drugs may injure the liver in at least three ways, and possibly more. The distinction between the mechanisms involved is of more than academic interest, since it provides the only rational basis we have for designing screening methods for testing the potential dangers of new drugs, and for planning surveillance methods in patients receiving drugs that are known to produce liver injury. Few drugs are true hepatotoxins, and those that are have largely been abandoned. As examples, carbon tetrachloride, chloroform, and massive doses of arsphenamine may be cited. Characteristically, these agents attack the liver directly by inactivating essential enzyme systems, leading to necrosis and death of parenchymal cells. The features that characterize this type of hepatic injury may be summarized as follows: First, these drugs will produce hepatic injury in all individuals, provided a sufficient dose is given. Second, the lesions are always reproducible in experimental animals. Third, both the occurrence and the extent of the lesions are clearly related to the amount of drug and the duration of its administration. Finally, there is a very definite latent period, usually

quite short, between the administration of the drug and the appearance of liver injury.

In contrast, most drugs that produce hepatic injury do so only indirectly, by what is generally considered to be a hypersensitivity reaction. Characteristics of this type of liver injury may be summarized as follows: First, only a very small proportion of individuals who receive the drug, no matter what the dose, develop hepatic injury. Second, the lesions are not reproducible in any experimental animal. Third, the latent period between the onset of drug therapy and the appearance of liver lesions is highly variable; thus, injury may appear after the first dose or not until after several months of therapy. Fourth, there is no relationship between the appearance of the lesion, or its extent, and the dose of drug used. Finally, the hepatic lesions usually follow, or are associated with, other manifestations generally considered indicative of hypersensitivity. These include fever, rash, lymphadenopathy, arthralgia, disturbances in kidney function and disturbances in the hematopoietic system, including eosinophilia. While such reactions are considered manifestations of hypersensitivity, it should be recognized that they differ from the classical types of hypersensitivity, such as serum sickness, or experimental hypersensitivity in animals. The chief differences are: First, it is rarely possible to demonstrate circulating antibodies or skin sensitivity. Second, the latent period from injection or ingestion of antigen to the appearance of a reaction is highly variable; and third, characteristics of the reaction may vary from individual to individual, and also from drug to drug. Nevertheless, I believe that ultimately it will be shown that drug reactions are a form of hypersensitivity, although it is highly probable that they differ from the classical type, due to foreign proteins. It is possible, of course, that further research may reveal some type of enzymatic defect, such as has been demonstrated in the red cells, to account for some types of hemolytic reactions.

Two generalizations about drug sensitivity are worth bearing in mind: First, any drug that produces liver injury in man but fails to do so in animals is almost certainly a sensitizing agent rather than a hepatotoxin. Second, if a drug produces other manifestations of hypersensitivity, such as rash or fever, it can be predicted with reasonable certainty that sooner or later it will also produce hepatic reactions in some individuals.

A third, rather uncommon, type of drug reaction is seen following the administration of drugs such as methyl testosterone and norethandrolone. In this instance one finds that, by giving a sufficiently large dose, one can usually produce hepatic changes in most individuals. This suggests that these compounds are hepatotoxins. However, in contrast to the usual hepatotoxins, they fail to produce lesions in animals. We shall hear more about this from Dr. Popper and Dr. Schaffner, who are interested in this problem, and who may have some evidence to the contrary. On the other hand, it is inappropriate to call these sensitizing agents, since in none of the reactions reported thus far have other manifestations of hypersensitivity been described.

Finally, a fourth possible type of drug hepatitis that comes to mind is that seen as a complication of treatment with iproniazid (Marsilid), cinchophen, and pyrazinamide. In this disorder the lesions resemble those seen in massive hepatic necrosis or subacute hepatic necrosis due to the hepatitis virus. This raises the question whether or not these drugs precipitate a latent infection in carriers of the hepatitis virus, or render them more susceptible to intercurrent infections. However, in a number of patients who have developed such reactions, other manifestations of hypersensitivity have been encountered. This would suggest that these represent hypersensitivity reactions, although the morphological picture, as we shall see from Dr. Popper's slides, is somewhat different from that seen in other drug reactions. Also, a number of investigators have carried out hemagglutination tests in such patients with negative results, which also suggests that these are not due to acute viral infections.

With this introduction I shall call on Dr. Popper, who will discuss the pathology of the different types of iatrogenic hepatitis seen in man.

DR. HANS POPPER: To the pathologist a series of different hepatic lesions present themselves in conditions which we assume to be iatrogenic, that is, that the treatment of the physician has induced the lesion. To fulfill the request of Dr. Klatskin, I would like to present to you the different features as we see them, either in biopsy specimens or on the necropsy table. I shall not go deeper into the pathogenesis of these lesions at this time.

I think all of you are well acquainted with the picture of serum hepatitis, and Dr. Havens will discuss it in more detail. Here is a biopsy specimen and the features of major importance are: first, the great varia-

tions in cytoplasmic and nuclear characteristics in the liver cells, from cell to cell, each cell differing from the next; second, the acidophilic bodies; and third, the conspicuous mesenchymal reaction quite variable in degree throughout the slide. If the lesion involves all liver cells at one time, the patient dies with the fulminant type of hepatitis, the so-called yellow atrophy. Those who live a little longer may show liver cells trying to survive and regenerating, and surrounded by a severe mesenchymal reaction; in addition, intrahepatic bile stasis is noted. This lesion has also been demonstrated for comparison with the various drug-induced lesions which I now want to present.

Dr. Klatskin has reminded us of a group of drugs which are really poisonous, usually interfering with known metabolic processes. They don't fascinate us so much, as we know the implications of their administration and of their overdosage. The effects have a clear dose relation, and they can be reproduced in animals. An example is the carbon tetrachloride intoxication with centrolobular fatty metamorphosis and necrosis and ballooning of the liver cells. This type of drug-induced hepatic injury presents few diagnostic problems except to emphasize the importance of looking carefully into the history to establish whether the patient took the drug.

More problematic are the lesions which I want to present now, and which offer the real problems from the point of view of diagnosis and mechanism. The classical example today is chlorpromazine (Thorazine) jaundice. Histologically, in the fully developed stage, liver cell damage is not conspicuous but two other features predominate: 1) severe bile stasis, mainly in the centrolobular zone, and 2) portal inflammatory reaction. The latter consists of a variety of mononuclear cells intermixed with segmented leucocytes, many of them eosinophils. The cells are arranged around proliferated and altered bile ductules or cholangioles. This explains the name, chosen by many, of "hyperergic cholangiolitis" for this lesion. It also has been assumed that this produces a mechanical obstruction to the bile flow and thus explains the cholestasis. However, there are other cases of chlorpromazine jaundice in which this portal inflammatory reaction is absent. This is particularly true of fatal chlorpromazine jaundice, which is very rare. I know of nine cases in all, and in these the bile stasis was particularly severe. It seems to be actually the cause of death. However, in these instances no "hyperergic" or other type of portal reaction is noted. This makes it

quite clear that two independent phenomena seem to exist in chlorpromazine jaundice. One is the portal inflammatory reaction, which is transient and apparently related to the manifestations of the general hyperergic reaction to which Dr. Klatskin made reference. The second phenomenon is intrahepatic cholestasis, without apparent mechanical obstruction. This, I hope, Dr. Schaffner will discuss later.

Other drugs produce the same alteration; for instance, in biopsies of patients with jaundice developing in the course of treatment with chlorpropamide (Diabinese), both portal inflammatory reaction and bile stasis without significant liver cell damage is again noted. In contrast, in jaundice following treatment with another group of drugs exemplified by methyltestosterone or its derivative norethandrolone (Nilevar), the cholestasis is not associated with conspicuous liver cell damage nor with portal inflammatory reaction; that means the so-called hyperergic reaction is not found. Also, in the jaundice occurring during treatment with para-aminobenzoic acid, severe portal inflammatory reaction is present. As a matter of fact, we have seen biopsy specimens of a few patients with reactions during such a treatment in which the portal inflammation was quite marked in the *absence* of jaundice. This may hold true for other drugs. We have seen, for instance, after the administration of succinyl-sulfathiazole (Sulfasuxidine) and neomycin, severe so-called hyperergic cholangiolitis without any jaundice. Therefore, we have to assume that this type of portal reaction does not produce jaundice and that the intrahepatic cholestasis is an independent response to the drug. Whether it represents a hyperergic phenomenon, I do not know.

To the drug reactions presented so far, namely, the response to poisons, the cholestatic reaction and the portal inflammatory reaction, we now add a fourth group which morphologically resembles viral hepatitis and which, both clinically and in the laboratory, is separated from it only with difficulty. The most notorious recent representatives are the lesions following administration of the monoamine oxidase inhibitor, iproniazid (Marsilid). Histologically, we see in biopsy specimens of patients developing jaundice after iproniazid administration the same cell necrosis, acidophilic bodies and inflammatory reaction which is characteristic of viral hepatitis. I originally believed what Dr. Klatskin has already suggested, namely, that we deal here with an activation of the virus by the drug. I do not believe this any longer and

would rather assume that we have, in both instances, a hyperergic reaction, one to the virus and the other to the drug, both being histologically identical. This group of drug reactions can best be designated as hepatitic forms. This type of hepatitis has a grave prognosis. In some instances, death sets in rapidly and at autopsy an acute atrophy of the character of fulminant hepatitis is seen. In other instances, subacute atrophy with progression into postnecrotic cirrhosis develops in patients who die about two months after the onset of jaundice. I could add several more examples of drugs which, in apparently very low incidence, lead to a hepatitis with grave prognosis. For example, the cinchophen-induced hepatic lesions, of many years ago, seem to belong in this group, and recently pyrazinamide and zoxazolamine (Flexin) seem to have produced similar cases with very low incidence.

Summarizing, then, the lesions which we have shown can be divided into three types of drug reaction, if we omit the poisons: the hepatitic form, the intrahepatic cholestasis and the portal inflammatory reaction. Whether the last, which frequently complicates the cholestatic form, has any functional or clinical consequences, I do not know. The cholestatic form apparently has a much higher incidence than the others but is still quite unpredictable. The danger, as far as prolonged morbidity and fatality are concerned, is rather slight. The hepatitic form is extremely rare, the incidence, again, unpredictable, but in the few instances which have been observed, the mortality may be as high as 20 per cent.

MODERATOR KLATSKIN: Thank you very much, Dr. Popper. Dr. Havens will now speak on iatrogenically induced viral hepatitis.

DR. W. PAUL HAVENS, JR.: There are probably several viruses that cause hepatitis in man. However, our concern today is with that form of disease produced by the inoculation of hepatitis virus A or B, with major emphasis on the latter, since it is numerically more frequently involved. There are certain unique features of an epidemiologic, clinical and immunological nature about infections with virus B that are of considerable interest. Of importance, I think, for discussion is the completely arbitrary definition of serum hepatitis as a disease that is transmitted parenterally. Philosophically, it is not easy to accept the concept that it is dependent on contaminated needles for survival. It may be true, but there are other possibilities such as the suggestion of Dr. Joseph Stokes, in Philadelphia, that hepatitis virus B might be transmitted in utero from mother to child.

Historically, serum hepatitis is an old disease. It was probably first recognized in the latter third of the nineteenth century by Dr. Lürman, in Germany, who observed a large outbreak of jaundice following mass vaccination. Dr. Ruge, late in the nineteen twenties, reported similar occurrences in neosalvarsan clinics. However, the true recognition of this disease as an infectious one, associated with the inoculation of contaminated materials, was accomplished by Dr. Flaum, in Scandinavia, in 1926. You are well acquainted with the unfortunate experience that occurred in South America, and subsequently in our armed forces with the advent of yellow fever vaccine. The increasing use of human blood and its various products during the past two decades has compounded the problem.

There is not much known about hepatitis virus B. It is small, probably near in size to the poliomyelitis virus. It cannot be classified, however, as an enteric virus, since we assume its major form of transmission is by parenteral inoculation. A major feature, I presume, is its tremendous resistance to a number of physical and chemical agents, and it is this property that constitutes an important problem today. We know that it is transmissible to man in a serial passage, and we know that it evokes a rather equivocal sort of homologous immunity. The status of this immunity is certainly in some doubt. Another important problem created by this virus is the carrier state, and it is estimated that under certain circumstances at least one half of one per cent of the population may be regarded as carriers of hepatitis virus. There is little understanding of the rather curious symbiotic relationship that exists between the apparently healthy carrier and the "fellow-travelling" hepatitis virus; likewise, there is no appreciation of the factors potentiating a break in this equilibration that transforms the carrier into a patient with hepatitis. Dr. Popper hinted earlier that one possible explanation of this curious clinical relationship might be that the occurrence of serum hepatitis actually represents a hyperergic response to virus, rather than the direct effect on hepatic cells. In support of this are some interesting aspects of the onset of serum hepatitis that are reminiscent of hyperergic phenomena; i.e., the occurrence of arthralgia and urticaria in a goodly percentage of patients, and uncommonly, but often enough to make it worth one's notice, the occurrence of a purpuric rash. If clinical serum hepatitis be the result of an hyperergic response, it is conceivable that this is a response to some product of interaction of virus

and parenchymal hepatic cell rather than to virus itself. Dr. MacCallum, in England, some years ago suggested this possibility and, as you all know, the concept now enjoys considerable favor among many investigators of liver disease, particularly among those who are inclined to regard hepatitis as the result of an autoimmune mechanism.

I mentioned earlier that the immune status of serum hepatitis is rather an equivocal one. For example, only a small percentage of the thousands injected with yellow fever vaccine known to contain serum hepatitis virus came down with the disease. This at once raises the question as to whether there might be some natural or acquired resistance in a large percentage of the population to this virus. The suggestion that large doses of normal immune gamma globulin may modify serum hepatitis, if given during the incubation period, supports this theory. On the other hand, experiments with volunteers have had contradictory results, with both success and failure, in demonstrating homologous immunity. Among the possible explanations for these controversial findings are the following: exposure to this virus, particularly if it be dependent upon parenteral inoculation, is sufficient to evoke a widespread and vigorous immune response; the virus or strains of virus have little capacity to evoke an immune response; there may be multiple strains of virus involved, with little cross-immunity.

(Slide) An illustration of the complexity of immunologic relationship is furnished in this slide representing the clinical course of three attacks of hepatitis at yearly intervals in a narcotic addict. These were not recurrences, because we had evidence of apparently complete recovery, demonstrated by laboratory data and biopsy of the liver, following each attack. It is possible that he was infected by different strains of one virus that evoked no cross-immunity or that he was infected at least once by hepatitis virus A and then two more times by strains of virus B. His frequent participation in groups practicing the self-administration of narcotics with unsterilized instruments is a perfect background for the development of this situation.

Serum hepatitis is world-wide in distribution, and it is of interest that co-existence between this disease and naturally occurring infectious hepatitis is quite possible. Thus, hepatitis virus B can equilibrate itself not only with man but also apparently with virus A in the same community.

(Slide) This slide illustrates the co-existence of virus A and virus B

in outbreaks of hepatitis in a venereal disease clinic in Vienna reported by Dr. Wewalka. In the first year of the outbreak, the majority of cases occurred 16 to 20 weeks after beginning parenteral therapy. Improper sterilization of syringes and needles was blamed for what seemed to be a perfectly *bona fide* outbreak of serum hepatitis. In the following year in the same clinic, there was an outbreak with two peaks of greatest incidence, one occurring four to eight weeks after starting parenteral treatment, and the second occurring after 16 to 20 weeks. The suggestion here is strong that more than one virus was being transmitted, and since we know that virus A can be transmitted parenterally, it would seem a good example of co-existence.

Major problems today in serum hepatitis are: (a) the frequency and duration of the carrier state and our inability to detect it; (b) the widespread use of human blood and its products and the failure of our methods to sterilize them.

(Slide) Very briefly, here are tabulated the results of experiments in volunteers to determine the resistance of virus B to a variety of physical and chemical agents. It survives heating to 60° C. for four hours but is inactivated at ten hours. The latter is a very happy circumstance, since the commercial production of human albumin includes this procedure. Exposure to varying amounts of ultraviolet light, tricresol, phenol, ether, Merthiolate, and nitrogen mustard failed to inactivate the virus. However, sulfa-mustard and beta-propiolactone, in concentrations too large to be appropriate for use in blood, inactivated the virus. At present, there is hope that it may be possible to combine two or more of these physical and/or chemical agents in such a way that treatment of blood or its products with them will result in inactivation of virus.

I would like to mention the interesting work of Dr. Allen, in Chicago, who, with Dr. Ross Gauld, has done follow-up studies on large numbers of patients who received plasma stored at 80° to 90° F for six months. The results would, I think, seem to indicate quite clearly that plasma treated in this way no longer has sufficient viable virus to produce hepatitis with jaundice. However, it might be stated that the danger of contamination of such plasma, the possibility of changes in proteins, and the prolonged period of treatment required make this method less than desirable as the way to sterilize plasma of hepatitis virus.

(Slide) This last slide tabulates the status of human blood and its

products, in relation to safety in use, where possible contamination with hepatitis virus is concerned. As far as we know at the moment, fibrin foam, gamma globulin prepared by ethanol fractionation, and salt-poor albumin have not been associated with the production of hepatitis in recipients.

MODERATOR KLATSKIN: Thank you, Dr. Havens.

I shall now ask Dr. Schaffner to discuss the differential diagnosis of drug-induced hepatitis.

DR. FENTON SCHAFFNER: I would like to confine my remarks first to some clinical aspects of the problem and then describe some of the investigations we have carried out in patients with drug-induced hepatic injury, and some of the ones we have done in animals.

In general, to make a diagnosis of drug-induced injury, one should have a history of ingestion of a drug. Sometimes this is difficult to obtain. Patients and/or physicians will withhold information that a drug has been given. This has been more likely to occur recently with some of the drugs causing the more serious reactions. We question every patient who comes to the hospital with jaundice as to what drugs he has taken. If a drug which has been reported to cause jaundice has been given to a patient, we then entertain the possibility that such a drug has indeed produced some hepatic injury.

Following the histologic studies of Dr. Popper, we have divided the injuries into two types. The first one presents the problem of cholestasis following the ingestion of certain drugs such as chlorpromazine, methyl testosterone, norethandrolone, chlorpropamide, and some of the sulfonamides. In this group the main differential diagnosis is between drug-induced cholestasis and extrahepatic biliary obstruction. The differential diagnosis is probably one of the most difficult to make in the clinical practice of medicine, and sometimes it becomes necessary to ask the surgeon for help. For such a patient with jaundice, dark urine, light stools, pruritus, fever, right upper quadrant tenderness and, on laboratory examination, with elevation of serum alkaline phosphatase and no evidence of liver cell damage, we must at least outline a course of action to take in making the differential diagnosis. X-ray studies of the gastrointestinal tract are important; and pancreatic function tests with secretin, plus biliary drainage, in an attempt to rule out diseases of the extrahepatic biliary tract, have been used with some success. In general, the differential diagnosis is made for us by time, because, if one

waits long enough, the patients with drug-induced cholestasis will usually recover. The other means of making such a differential diagnosis will be discussed by Dr. Shay.

After the patient has recovered, various challenge tests may establish a relationship between the injury and the administration of the drug.

The separation of the hepatitic type of hepatic injury, caused by iproniazid, from viral hepatitis, cannot be made at all on either clinical or on laboratory grounds, nor, as Dr. Popper has said, on histologic grounds. Here again, history of ingestion of the drug is important.

Recently we saw a patient who died with jaundice following the administration of beta-phenylisopropylhydrazine. We suspected, but could not prove, that the drug produced a lesion similar to that caused by iproniazid. The only way one can establish a causal relationship is to collect enough cases to suggest that this may be so. In the individual case such a differential diagnosis is very difficult.

I might add one point in the differential diagnosis of cholestasis. A woman, at present on the wards of our hospital, developed mild diabetes and was given chlorpropamide. She developed typical cholestatic jaundice, and under ordinary circumstances it would have been difficult to differentiate between chlorpropamide jaundice and extrahepatic biliary obstruction. However, in this case, on physical examination there seemed to be a mass in the right upper quadrant, and the finding of a mass should outweigh all laboratory tests and probably also the history.

In the search for mechanisms of production of these drug-induced hepatic injuries, and in the hope of finding some differential diagnostic tool, we examined under the electron microscope many of the same specimens Dr. Popper showed you. I would like to indicate a few of the things we have done, and tell you about some of the conclusions we have reached.

In the normal bile canaliculus seen in a biopsy specimen from a patient of Dr. Shay, between two or three liver cells, magnified on the screen about 50,000 times, there are small fingers, called microvilli, projecting into the lumen. Bile is secreted by the liver cells directly into the bile canaliculus.

In the patient with chlorpropamide jaundice, the bile canaliculus no longer has as many nice, long, fingerlike microvilli. This finding is characteristic of cholestasis in general, whether there is intrahepatic or extrahepatic obstruction. The normal microvilli either become short-

ened and stunted or disappear. The bile canaliculus may or may not be dilated, and it may or may not rupture into the tissue space to produce the phenomenon of regurgitation. However, the only characteristic which seems to be closely correlated with the development of jaundice is this alteration in the canalicular membrane of the liver cell. We feel that this is the basis of the phenomenon of cholestasis.

We knew that norethandrolone had produced jaundice in a number of cases that we studied previously, and we also knew that it had caused bromsulfalein retention in almost every case. In order to see the mechanism of production of this type of jaundice, we gave the drug to four patients and some rats and examined biopsies of their livers under the electron microscope.

Norethandrolone produced dilation of some bile canaliculi in man. However, other bile canaliculi, very closely associated with the dilated ones, were quite normal, suggesting that the effect apparently is somewhat selective to certain bile canaliculi, although the reason for this is not clear. I suspect that clinical jaundice does not become apparent until a sufficient number of canaliculi are involved.

In a rat given norethandrolone in doses considerably higher than that given to man, bile canaliculi were again dilated and abnormal. The rest of the liver cell, nucleus, nucleolus, mitochondria, the endoplasmic reticulum, which is the synthesizing portion of the cell, the glycogen content, and the sinusoidal borders were all normal. Apparently, norethandrolone has some specific effect upon the canalicular membrane.

In viral hepatitis cholestatic features sometimes develop. Most bile canaliculi are normal, but some are quite dilated and show only a few rather stunted microvilli. I believe that the cholestatic component of viral hepatitis is related to the number of canaliculi involved. Before the meeting, Dr. Klatskin and Dr. Havens were discussing virus particles in viral hepatitis, and I have included one slide of what has been purported to be virus particles.

In some liver cells, along the endoplasmic reticulum, there are small particles replacing the normal ribose nucleoprotein granules. Instead of being normally globular, the altered particles are larger and seem to have some internal structure to them. This is the only example that I have in my own material similar to what has been called the viral particle of virus hepatitis. I certainly have no proof of this.

In iproniazid jaundice I have not seen such particles. I have had only

one case to examine, and the abnormality here appeared to be in the mitochondria and in the endoplasmic reticulum. Surviving cells were seen next to necrotic cells. In the necrotic cell, the mitochondria had disappeared, the endoplasmic reticulum was broken up and the nucleus was in process of disappearing. Whether the electron microscope will be able to differentiate iproniazid injury from viral hepatitis, I don't know. I would like to suggest that it may, but we need more cases to find out about this. I suspect we shall not get them because most physicians are using less iproniazid.

In conclusion, I would like to say that we can make the diagnosis of cholestasis with the electron microscope which the physician can do at the bedside. We cannot make the differential diagnosis with the electron microscope between extrahepatic biliary obstruction and intrahepatic cholestasis. We probably can at least attempt to make a differential diagnosis between the necrotizing form of hepatic injury from viral hepatitis.

MODERATOR KLATSKIN: Thank you, Dr. Schaffner.

The last of our panelists to speak is Dr. Shay, who will discuss screening methods in the early detection of drug-induced hepatitis.

DR. HARRY SHAY: In his introductory remarks, Dr. Klatskin indicated the serious nature of the problem we face with hepatotoxic effects of drugs on the liver. From all indications, as the organic chemist continues to devise new and complex organic radicals for human consumption, this problem may increase rather than diminish. Added to this is still another problem, one of exact diagnosis in cases of cholestatic jaundice. It appears, therefore, that if we are to hope for much relief in this area, we must seek to devise some approach to the prevention of these "hepatotoxic" reactions. Unfortunately, a method that is foolproof is not available, but we do think that an approach, as it relates to cholestatic jaundice, is possible. Thus far, it appears that cholestatic jaundice produced by drugs is essentially a sensitization process, and in its development biochemical changes in liver function, that may be detected before, appear—a situation that unfortunately does not seem to be true for those drugs directly hepatotoxic. Perhaps I can best present these effects by showing some results with chlorpromazine, a liver-sensitizing drug, and with iproniazid (Marsilid), a direct hepatotoxic agent.

(Slide) We thought a prophylatic approach for chlorpromazine jaundice might be possible, since observers reported certain recurrent

findings, as far as the liver function profile was concerned. These, when jaundice developed, consisted of elevated phosphatase, elevated cholesterol, and very often, even after the jaundice had subsided, an increased bromsulfalein retention. In following patients on chlorpromazine we considered whether we might not pick up these changes before actual jaundice developed. Accordingly, studies were conducted in individuals receiving chlorpromazine, a liver profile being done before the drug was started, and biweekly for a period of three to four weeks. This slide represents the results in an individual showing the bilirubin, alkaline phosphatase and bromsulfalein in whom no change was produced by the administration of the chlorpromazine. All values remained normal throughout. Incidentally, may I call your attention to the serum alkaline phosphatase values which normally vary within very narrow limits over a long period of time for any one individual.

(Slide) This slide shows the result of chlorpromazine administration in an individual started on April 16, in whom no change in total bilirubin or in serum alkaline phosphatase occurred until April 30, when a very sharp rise in phosphatase appeared, without any alteration in bilirubin. The drug was discontinued, and the serum values returned to normal by May 14. On June 18, the drug was again started, without further effect on serum alkaline phosphatase.

(Slide) Not only can these changes occur with alkaline phosphatase, but glutamic oxalacetic transaminase levels will behave very similarly. We believe that there is good evidence that these changes are the result of a sensitization of the liver by chlorpromazine.

(Slide) At one point in the study we had to determine whether continuation of the drug would produce jaundice in all patients who showed these serum enzyme changes. In this individual, when the elevation in phosphatase and bromsulfalein retention occurred, the drug was continued cautiously. In spite of this, the value for both enzymes returned to normal. The abnormal values in phosphatase, and bromsulfalein retention and transaminase will occur in roughly about 25 per cent of the patients who receive chlorpromazine. Fortunately, however, the vast majority of these patients become desensitized even though the drug is continued.

(Slide) These data indicate the existence of a sensitization mechanism and how this effect was related to the chemical structure of chlorpromazine. This woman became jaundiced after a course of chlorpro-

mazine, recovered from it and was warned not to take any additional chlorpromazine. However, a year later she decided to take three tablets of chlorpromazine in the course of the day, and this was followed very rapidly by chills and fever, and within two days by hyperbilirubinemia, elevated phosphatase and elevation of transaminase (SGOT and SGPT). She was allowed to recover and was then given promazine. The only difference between chlorpromazine and promazine is the addition of chlorine in the 2-position in the promazine molecule. Given the promazine in the same daily dose as the chlorpromazine, nothing happened. Promazine was continued for a week, no untoward reaction developed. However, when she was given 5 mg. of chlorpromazine in a capsule, symptoms appeared within twelve hours, and on the following day, while her urine was still negative for bile, a very sharp rise in serum transaminase, and subsequently in phosphatase, took place.

(Slide) We then administered a compound in which the chlorine was replaced by an acetyl group, and there was no reaction. Compazine, which has the chlorine intact in the 2-position, but a lengthened side chain, also produced no effect. However, when chlorpromazine sulfoxide, the major metabolite of chlorpromazine in the body, in which the molecule is not changed materially except for the addition of a loosely attached oxygen to sulfur, was given, a very rapid development of a reaction occurred. The addition of the chlorine in the 2-position in the promazine molecule appears to be responsible for the antigenicity for which chlorpromazine is responsible.

(Slide) These results illustrate what Dr. Popper emphasized; namely, our inability to differentiate iproniazid hepatitis from infectious hepatitis. The liver function profile is indistinguishable from that commonly seen in ordinary viral hepatitis. In the case of chlorpromazine screening, the patient's response, by serial study of serum alkaline phosphatase, during the first three weeks of therapy should make the prevention of chlorpromazine jaundice possible. For direct hepatotoxic agents, such as iproniazid, transaminase determination would be more valuable. However, with these compounds, one cannot be certain whether the liver damage would still be reversible.

MODERATOR KLATSKIN: Thank you, Dr. Shay.

A number of questions have been submitted by members of the audience, some of which, I think, have already been answered. I shall take them in the order that I hold them in my hand.

This one says that *phenobarbital has been found to induce jaundice. If so, what are the pathological changes in the liver?* I myself have seen several phenobarbital reactions associated with fever, skin reactions, plus hepatitis. In at least one instance, in a seven-year old child, this went on to progressive hepatitis and produced cirrhosis. In line with what I said previously, I think any drug that produces a sensitization reaction in the skin, bone marrow or kidney, can be predicted to produce a lesion in the liver sooner or later, although drugs do show variations. Thus, some drugs produce lesions in the kidney and bone marrow more often than in the liver, while others attack the liver more commonly.

This is one for Dr. Popper. *Are there any changes in the head of the pancreas in drug-induced hepatitis?*

DR. POPPER: I am not aware of any. Obviously, the pancreas does not lend itself as well to biopsy studies as the liver. In the two instances of iproniazid jaundice and the two of chlorpromazine jaundice, in which I saw the entire autopsy material, the pancreas was normal.

DR. SCHAFFNER: The pancreatic function is also normal in those cases.

MODERATOR KLATSKIN: Question: *What are the guides for prognosis in iproniazid hepatitis, and how long will acholic stools be expected to last?*

DR. SCHAFFNER: I think that probably the best guide to prognosis is the clinical status of the patient. If the patient is comatose, or signs of ammonia encephalopathy with the flapping tremor seem to be progressing and liver-size is rapidly shrinking, I think the prognosis is very poor. We have nothing better to offer, unfortunately. As far as laboratory changes are concerned, to go along with the clinical picture, a rising blood ammonia level is a bad prognostic sign. Probably precipitously falling bilirubin level, without clinical improvement, and decreasing serum alkaline phosphatase activity, as discussed before, are also bad prognostic laboratory signs.

What was the second part of the question?

MODERATOR KLATSKIN: *What is the expected duration of acholic stools in iproniazid hepatitis?*

DR. SCHAFFNER: I think this is exactly the same as in viral hepatitis. It varies.

MODERATOR KLATSKIN: I think it should be added that liver biopsy often is of great help in evaluating the prognosis. We have been surprised, not only in drug hepatitis but also in viral hepatitis, to find

patients who look remarkably well, but who show massive hepatic necrosis on biopsy.

Here is another question for Dr. Shay: *What therapy do you recommend for norethandrolone, methyl testosterone and chlorpromazine jaundice?*

DR. SHAY: As far as specific therapy is concerned, I don't know of any. Discontinuing the drug is probably the best approach to the problem.

DR. SCHAFFNER: May I modify the question to get a little further discussion? *There have been many cases in which jaundice and the other findings have persisted for long periods, making us feel quite uncomfortable and uneasy. What do you do then?*

DR. SHAY: I have seen that occur with chlorpromazine. As a matter of fact, we followed some patients with chlorpromazine jaundice in whom the picture strongly aroused the suspicion that they might be going on to a biliary cirrhosis. We were just as helpless then in altering the course as we were before. Fortunately, such cases appear to recover with time.

MODERATOR KLATSKIN: As a rule, jaundice of this type is asymptomatic, and the major problem, as far as the physician is concerned, is the exclusion of obstructive jaundice due to some mechanical cause. One thing that has been tried with equivocal success has been the use of the corticosteroids as a diagnostic test. If the patient has prolonged jaundice due to norethandrolone, or methyl testosterone one occasionally sees a dramatic fall of the serum bilirubin to normal in response to steroids. However, if jaundice does not clear completely, one should bear in mind that partial clearing may occur in obstructive jaundice also. Accordingly, the use of corticosteroids has not been very helpful in diagnosis.

DR. HAVENS: I would like to add that I think doing this adds to the confusion and makes the differential diagnosis of the cause of the jaundice more difficult. One ends up, in 99 per cent of the cases, with complete obfuscation of the situation, necessitating a fresh start from scratch.

MODERATOR KLATSKIN: Several questions have come from the floor *regarding the occurrence of jaundice in association with the use of other mono-amine oxidase inhibitors. Have any of the panelists had any experience with such drugs?*

DR. SCHAFFNER: Just one, with beta-phenylisopropylhydrazine that I mentioned before.

DR. POPPER: To my knowledge no others have been reported.

MODERATOR KLATSKIN: I remember that at the iproniazid conference held in New York about a year ago, which Dr. Popper and I both attended, there was a great deal of talk about whether it was the enzymatic activity of these inhibitors that accounted for liver injury. No evidence implicating an enzymatic disturbance as the cause of the jaundice was presented. My own opinion is that iproniazid induces a hypersensitivity reaction and is not a true hepatotoxin.

Another question directed to our panel is: *Can quinidine act as a hepatotoxin?* I myself have seen anaphylactic reactions to quinidine and to quinine, that is, collapse and vasomotor disturbances of other nature, but I have not seen rash or jaundice.

DR. HAVENS: Purpura is not uncommon following quinidine. I have not seen hepatic disease.

DR. POPPER: To cut my own talk short, I left out one group of drug reactions, namely, the nonspecific hepatic changes which develop with almost any drug reaction in any other organ, for instance, kidney, myocardium or bone marrow. Under these circumstances, a so-called nonspecific reactive hepatitis develops and I would suspect that such may have been found on liver biopsy in the quinidine cases. Moreover, in drug reactions associated with systemic shock, we have reflection of this in the liver in the form of entirely nonspecific centrolobular necrosis.

MODERATOR KLATSKIN: In the remaining few minutes, I myself would like to ask a few questions of the panelists. *A review of the scattered reports on drug-induced hepatitis suggests that women are affected more commonly than men. Does this imply that women are more susceptible to drug reactions, or is the difference due to the greater use of drugs among women? Dr. Shay?*

DR. SHAY: I am afraid I am not in a position to clarify the question. I doubt if there is a difference in susceptibility. It is probably true that perhaps more women are exposed to these drugs than men, but I honestly cannot contribute anything very tangible.

MODERATOR KLATSKIN: Most people who have had experience with drug reactions have been impressed with their greater frequency in women. This is generally attributed to the greater use of drugs by

women. However, I have gone through the literature collecting cases at random, looking particularly for reactions to drugs that are likely to be used equally by both men and women, such as antituberculous and anti-epileptic drugs. It is remarkable that reactions are always more common in women. It may be significant that women are also more susceptible to the chronic progressive form of hepatitis.

DR. SCHAFFNER: It is interesting that it is the older women, more often post-menopausal than pre-menopausal, who have this. One wonders just what effect sex hormones have in producing this condition.

MODERATOR KLATSKIN: In our experience the disease occurs at all ages.

DR. POPPER: If one surveys the results of experimental administration of hepatotoxins or carcinogens, one almost invariably finds sex differences. It would be surprising if the human were an exception.

DR. SHAY: One might throw onto the heap another situation that we know nothing about etiologically, and that is primary biliary cirrhosis and its frequency in the female.

MODERATOR KLATSKIN: One last question, because I think we are running over the allotted time. It is a question frequently raised by physicians. *Is there any evidence that patients with underlying liver disease are unusually susceptible to reactions? How do you feel about that Dr. Popper?*

DR. POPPER: In the relatively large number of cases of iproniazid jaundice, which I have had the opportunity to study histologically, I think more than 40 cases, there was only one in which morphologic evidence of pre-existing damage to the liver was noted. This is lower than what one would expect in the population at large. On the strength of that, I do not believe that patients with underlying liver disease are necessarily more susceptible to drug-induced liver injury.

MODERATOR KLATSKIN: Do the other panelists have any opinions on this point?

DR. HAVENS: In the treatment of alcoholics with chronic hepatic disease, there is no indication that a greater than normal percentage of them are predisposed to untoward reaction to the drugs as manifested by jaundice. Whether they are more likely to have subtle changes in hepatic function, I do not know.

DR. SHAY: That has been our experience too.

MODERATOR KLATSKIN: The only exception that I can think of is the

regular occurrence of jaundice in patients with chronic liver disease, who are given methyl testosterone, or norethandrolone.

DR. SCHAFFNER: We had the interesting experience of taking biopsies from a group of 28 patients before and after the administration of norethandrolone. Those that had nonspecific hepatic changes beforehand did not seem particularly predisposed to develop cholestasis, and indeed in some of them the nonspecific changes even improved following administration of the drug.

DR. HAVENS: It has been very interesting to me, Dr. Klatskin, to see patients who have failed to recover from viral hepatitis being treated with norethandrolone. I have been impressed with the possibility that this might be a rather dangerous thing to do.

MODERATOR KLATSKIN: I think there is no further time left for discussion. I thank the members of the panel for their contributions.

THE GLORNEY-RAISBECK FELLOWSHIP IN THE MEDICAL SCIENCES

The Glorney-Raisbeck Fellowship in the Medical Sciences for the academic year beginning July 1, 1962 will be awarded by the Committee on Medical Education of The New York Academy of Medicine for one year of research and/or study in any field of medicine or its allied sciences. Under circumstances deemed appropriate by the Committee, the Fellowship is renewable on a year-to-year basis for two additional years.

The Fellowship, which carries a stipend of $6,000, is open only to holders of the M.D. degree who have demonstrated potential for productivity in research and teaching. In general, preference will be given to physicians from the Greater New York area.

A candidate should be prepared to give assurance that he will have an institutional appointment in the United States which will enable him to carry out the objectives of his program of research and/or study. Such institutions will be encouraged to supplement the Fellowship stipend. Candidates also should be prepared to be interviewed by the Committee (out-of-town candidates at own expense).

Deadline for receipt of applications is *December 1, 1961.*

Requests for application forms and additional information should be addressed to:

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ANNUAL REPORT OF THE EXECUTIVE SECRETARY TO THE COMMITTEE ON PUBLIC HEALTH*

H. D. KRUSE

In old China the first question that was asked on an official call was, "What is your glorious age?" If the reply was an apologetic "27" or "28", the inquirer gave comfort by saying, "You still have a glorious future and one day you may become old." As a person was able to report a higher and higher age, his enthusiasm grew. For, when his answer was an age over 50, he was treated with veneration. Thus, persons looked forward with great anticipation to the celebration of their 51st birthday.

So the Committee on Public Health, now entering upon its 50th year, is on the threshold of its glorious period. At this time it is sufficient just to take note of its semicentennial since it will be suitably celebrated on another occasion.

In view of this anniversary it is fitting in this annual message to examine the concept of a committee, its structure and function; to compare the Committee on Public Health with the abstract prototype; to touch upon the highlights of this Committee's activities during the past year; and finally, to discuss one problem which is awaiting solution.

From time to time I have engaged in a bit of banter about committees and their own inimitable mode of operation. It has always seemed to me that an occasional self-inflicted jest was salutary in warding off any threat of pomposity. But in any serious attack against the utility of committees I would be the first to speak in their defense.

Recently Warren Weaver in an article entitled *Report of the Special Committee*, dropped a suggestion for simplifying the procedure by which various agencies reach decisions. It is a mildly satirical commentary on the *ad hoc* committee or subcommittee. He complains that their long reports are so technical as to be unintelligible and that only the usual summary report brings clarification and enlightenment. What he virtually proposes in the interest of promptness, efficiency and economy is the elimination of special committees and their studies.

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He foresees that deprivation of the technical section in a report will produce an agonizing wrench for the experts. For whereas a tea is described as a social event designed to give minimum pleasure to the maximum number of persons, the technical section of a report gives maximum pleasure to a minimum number of persons. As a replacement for the committee he has provided a standard universal form for a summary report suitable for any subject.

I have no intention of spoiling Weaver's pleasantry with a serious rejoinder. Although I have become something of an authority on the points of weakness in operation by a committee, I much prefer to dwell upon its distinctive points of strength.

Definitions, according to John Mason Brown, are verbal girdles that will neither uphold nor contain the whole truth. But, for want of a better foundation form, I must resort to this rhetorical device. "Committee" is a generic name for a group appointed or chosen by a larger number to give special attention to some matter or to perform some service. With such latitude and generality it is obvious that committees vary in type, function and size. They serve many purposes and perform many functions. One type is equivalent to a board, another is a working group. Committees also differ in their function: advisory, consultative, study, policy-making, and technical. Their size depends upon their type and function. Although some tasks are not appropriate to a committee, others it does superbly, perhaps better than they can be done by any other means.

In general, a committee is formed to do what a larger body would do only with difficulty. So boards have committees and committees have subcommittees.

"It is a thousand pities
And one of the worst of menaces
That all committees
—By a sort of parthenogenesis—

"Almost at once and as if to prove their worth
And quite impervious to snubs
Give birth
To not less than four little subs.

"Wherefore I have sometimes thought
That it might be very nice
If each newly formed committee could be caught
In time, and fitted with a suitable contraceptive device."

This process of subdivision is a necessity arising from the hazards, labor, difficulty and slowness of cross-communication.

Cooley has postulated that when John and Tom meet there are really six persons present rather than the apparent two. There is John's real self, known only to his Maker; John's idea of himself; and Tom's idea of John. Then, of course, there are the three corresponding Toms. Indeed, it is suggested that there may be actually twelve or more personality images present in any transaction ostensibly involving only two persons. For, in addition to the foregoing six, there is a series starting with John's idea of Tom's idea of John, and continuing into Tom's idea of John's idea of Tom's idea of John!

With such a complex relationship between two persons it may readily be imagined how complication is compounded in groups of ten, twenty or thirty persons. Indeed, mutual comprehension is said to be intrinsically so intricate that it is a wonder that agreement is ever reached in any group. Perhaps the strongest influence toward agreement is that it is just as difficult to reach a state of disagreement.

Fortunately through the years men assembled for discussion or action have developed a procedure, a form of group dynamics, that averts confusion and paralysis and leads to an effective and relatively expeditious outcome. So instead of being a road to chaos, a committee meeting, more often than not, is an avenue to decision.

Some years ago there was an advertising slogan which ran, "Such popularity must be deserved". Regardless of its defects, the committee system as a procedure has existed for a long time and, if anything, is more numerous today. Such hardihood and perpetuity must be deserved.

These are the strong points of a committee which are sometimes overlooked in critical appraisal:

For one thing, it is apt to give a middle-of-the road decision. If the membership contains a fair sample of personality types, this outcome is virtually predetermined. As Gilbert and Sullivan wrote:

> "Every boy and every gal,
> That is born into the world alive,
> Is either a little Liberal,
> Or else a little Conservative!"

By chance, a committee will almost certainly have some of each. Then there are the enthusiasts who are offset by the cautious. Actually, such a committee is a temperate zone warmed on the one side by the torrid

beams from ardent advocates, and chilled on the other by blasts from frigid intransigents. All the various types are essential ingredients for a balanced opinion. For, like the modern cigarette, a committee should have the choicest blend and an effective filter to give an opinion that suits the taste. True, on highly contentious issues the result may be a compromise. But if everyone is only partly satisfied and still partly disappointed with a decision, it can still be a useful and practical outcome.

Second, a committee's authority and prestige transcends that of any individual. A report with John Doe listed as the author carries only a fraction of the weight and impact as the same document under the name of a committee. Indeed, the whole of a committee's influence is even greater than the sum of its parts. If so many are of one mind, their opinion is bound to command respect.

These are the attributes that have justified the committee as a procedure: soundness of judgment, authority, and prestige.

Judged by these criteria, the Committee on Public Health has established its own particular niche. Its decisions have been sound, and it is a recognized authority. But in speaking of its prestige, I am in a quandary. Recently there has been such a flurry about measuring prestige that I am wary about claiming that the Committee's prestige is at an all-time high. Perhaps you will not challenge the statement that its prestige is amply high.

As for the record of the Committee during the past year, it might prove boresome to you to review in detail what you already know so well. But perhaps it would not be amiss to mention a few topics with which the Committee was preoccupied. As usual, they are characterized by wide range and variety.

One of the outstanding events was the dedication of the newly constructed Institute of Forensic Medicine. About 35 years ago the Committee was one of the influential bodies that pointed out the need for the Institute. Periodically since then, it has reaffirmed that position. Now, at long last, its recommendation has come to fruition. This illustrates that sometimes the impact of the Committee's opinions cannot be calculated at once, but must await even several decades.

For two years the Committee has been gathering information and deliberating on pharmaceutical advertising to the physician. Finally, it collected sufficient material and crystallized its attitude;

whereupon it entered into a series of conferences with the top executives of the pharmaceutical industry. These sessions are still in progress.

The Conference on Tobacco and Health held in conjunction with the Academy of Preventive Medicine drew a highly favorable reaction from those in attendance.

The Committee's report on the role of the physician in the adoption procedure has drawn nationwide requests for copies, and even for permission to reprint it.

In a totally different field, the Committee expressed its approval of the principle to incorporate health education on sanitation into a pilot demonstration to rid one of New York City's worst-infested areas of rats.

Turning to what are sometimes called the macabre aspects of medicine, the Committee recommended to medical schools ten steps for procuring sufficient cadavers for anatomical dissection, so that an impending crisis over a shortage could be averted.

Upon a request to take a stand in a legal action upstate over an allegedly unauthorized autopsy by a coroner, the Committee issued a report recommending replacement of the coroner system by the medical examiner system throughout the state, the training of sufficient medical examiners at the Institute of Forensic Medicine to fill the newly created positions, and the enactment of more precise and modern legislation on the duties of the office of medical examiner.

More recently, when the State Commissioner of Education issued a ruling granting parents the right to inspect school records, the Committee pointed out the possibly adverse effects of opening psychiatric records to scrutiny and strongly advised that these reports be kept on a confidential basis.

There were others who shared with you the work underlying these accomplishments: the staff. I am sure you would not want their efforts to go unmentioned. On your behalf I should like to voice appreciation of their talents and superb performance of duty.

This is a commendable record made by the Committee, but I am as fully aware as you that it could be even more impressive. This is not the occasion for excuses and explanations. But it is true that most of the reasons are external. One of the most important is that, in effect, the Committee is barred from undertaking an effective study of some of

the most pressing problems by the ancient English law against poaching. It is a not so trifling matter of jurisdiction. Today every ramification of medicine, health and hospitals has its committee or council.

But there is one major field that the Committee has entered—perhaps it is trespassing here too—pharmaceutical advertising. In turn, it provides a natural portal of entry to another area with troubles that are even more difficult to remedy. Closely related to pharmaceutical advertising, indeed the basis of it, is clinical testing. Here, it is admitted from all sides, the present quality is not satisfactory. Perhaps the first inclination is to criticize the pharmaceutical industry for unreliable claims on incomplete or invalid evidence. But the situation merits closer examination.

Through its research division a pharmaceutical company prepares a number of new compounds. These are given a preliminary test for their effect on animals. Usually, out of a number of compounds, only a few show enough promise to be submitted to intensive animal testing. The number is further diminished by the results of these intensive animal tests so that only one or two may be deemed of sufficient merit to subject them to the still more exacting clinical trial. This procedure is time-consuming with constant financial outlay. After all, a pharmaceutical company is a profit-making organization responsible to its stockholders. It has a tremendous investment in a new product because of the considerable overhead. Naturally it is anxious to get a return on that investment at the earliest possible moment. So the emphasis is on an early decision.

For present purposes it is not necessary to examine in detail all the possible ways in which clinical trials may miscarry or the results of them be mishandled. It is sufficient to recognize that some are disappointing, and to mention a few of the reasons. For one thing, the results may indicate that the product is inefficacious, or has hazardous side reactions. Secondly, other types of results are more frustrating to the pharmaceutical executive. Sometimes the clinical report is tantalizingly equivocal, or two clinicians of equal standing may submit contradictory reports on the same product. These results cast no reflection on the clinical tester. But there is another outcome of clinical testing that is not so exonerative. It occurs when a virtually worthless report is submitted. Sometimes the fault lies in the clinician's failure in performance of the test, at other times in the form of his report, either of which renders it of little value.

It is not improbable that in a number of clinical trials the sample of patients is neither adequate nor homogeneous. Hence, the evidence may not be as clear as is desired. Indeed, its validity may be in question. Nor, in some of the clinical testings, are the subjects always under close observation. For these and other reasons, it is usual for the early and preliminary reports on a new product to be modified after two or three years' experience with it. Not infrequently, as the new product is tried clinically with an ever-increasing sample comprising a variety of conditions, the notion of its efficacy undergoes discounting; limitations and shortcomings are revealed, and side reactions are increasingly reported. This is the too frequent outcome of testing, for which improvement is sought. Ideally, there should be thorough testing in the shortest possible time with results so reliable that subsequent revision is at a minimum. But in all fairness, it must be admitted in the light of practicality that this is a goal of perfection that may be unattainable under the best of circumstances.

For completeness the clinical test should reveal and demonstrate efficacy, side reactions, and contraindications of a therapeutic product. It is probable that the Food and Drug Administration will lay down such requirements for release of a new product. Observations on these points encompass such a wide range and variety that knowledge and training in several disciplines are needed. Ideally, it requires the services of a clinician, pharmacologist, experimental therapeutist, and statistician. Either the tester must have four skills in one skull, or there must be recourse to a team of specialists.

In designing the clinical test to obtain the right answer, it is necessary to ask the right question. Let me illustrate this point. Two priests were very ardent and inveterate cigar smokers. They smoked throughout the day, at least in private, until finally they began to have some concern as to whether this was really all right. So they discussed the matter and decided that maybe they should write to the Bishop. So each wrote to the Bishop and after an appropriate interval the replies came back. To their astonishment one got the answer "no" and the other got the answer "yes".

The one who got the answer "no" was unhappy about it and he consulted his colleague who asked, "What question did you ask?" The disappointed priest replied, "I asked, 'is it all right if I smoke when I pray?'" The other priest said, "Well, naturally, the Bishop said 'no'.

You didn't ask the right question." The priest who had received the negative reply said, "What did you ask?" The priest who had received the reassuring reply said, "I asked 'is it all right if I pray when I smoke?'"

In the conduct of the test it is necessary to know, or at least have some idea of, what to look for and where to look. It is an old maxim that the surest way to see something is to be looking for it. But it is equally important for the tester to have a highly developed perceptiveness that leads him to observe the seemingly insignificant significant, the inconspicuous and the unexpected.

In the planning of the test as well as in the analysis of the data, the usefulness of statistical methods, indeed their essentiality in many instances, is becoming increasingly realized. It is sometimes said that facts are stubborn, statistics are more pliable. But statistics too has survived repeated attacks by such derisive and belittling remarks and has become an indispensable tool in biological testing and assay.

Finally comes interpretation of the results with the necessity sometimes of distinguishing between a cause-and-effect relationship and association. It isn't always easy. Dr. Berry of Harvard relates an incident that illustrates the easier variety. In 1869 when Charles Eliot became President of Harvard, the medical school began to undergo a rapid and stormy transition from an independent proprietary school to a university institution. It marked the beginning of scientific medicine there. Changes such as higher requirements for entrance and introduction of collateral sciences were resisted; Henry Jacob Bigelow, a distinguished surgeon, was champion of the recalcitrants. Finally the battle went to the Harvard Corporation. At this Dr. Bigelow disdainfully exclaimed: "Does the Corporation hold opinions on medical education? Does Mr. Lowell know anything about medical education? Why, Mr. Crowninshield carries a horse chestnut in his pocket to ward off rheumatism. Is the new medical education to be directed by a man who carries a horse chestnut in his pocket to prevent rheumatism?"

Mr. Crowninshield was asked whether he did carry a horse chestnut in his pocket to protect him from rheumatism. He replied that he did indeed. And did it work? He thought it might be said that the horse chestnut was effective—in any event, it was a fact that he had had no attacks of rheumatism since he carried a horse chestnut in his pocket. Then he amplified his report by saying that what really amazed him

was the retroactive influence of the horse chestnut—for the fact was, he said, he had had no attacks of rheumatism before he started carrying the horse chestnut.

Recently, a committee of the National Academy of Sciences, appointed at the request of the Secretary of Health, Education and Welfare, "to review the policies and procedures used by the Food and Drug Administration in reaching decisions concerning the acceptance and certification of new drugs and the scientific soundness of the decisions made in recent years" submitted its report with eleven recommendations. One of the most significant of its recommendations was that the FDA should be given statutory authority to require proof of the efficacy as well as the safety of all new drugs. If put into practice the proposals in the report would constitute a step forward. Undoubtedly federal legislation is required which would extend and strengthen the authority of FDA. But beyond such governmental action, the success of clinical testing ultimately hinges on the performance of the medical profession.

Several measures would be helpful in meeting the generally acknowledged need for improvement in clinical testing. But above and beyond all the technical aspects, there should be well-defined plans for means of achieving adequate testing. For the crux of the clinical test is the tester. To reiterate, on the medical profession falls the responsibility for conducting satisfactory tests.

Achievement of adequate testing has two aspects: qualitative and quantitative. Some of the ingredients of qualitatively satisfactory testing have already been described; at present the quantitative aspects, i.e., the sufficiency of talent, is of equal concern. For, regardless of whether the testing is to be done by multi-skilled individuals or a group of various experts, such personnel is in short supply. By either approach there is not enough available qualified medical and scientific manpower to test the ever-increasing number of new or modified products from the pharmaceutical industry.

This is not an exhaustive critique of clinical testing but only a brief commentary on its present status and some of the problems which it presents. Besides the industry's impulse for expeditious testing and the shortage of qualified manpower, there is another and overriding concern: the protection of the public. It is the paramount consideration. Indeed it is the main justification for the Committee to focus its atten-

tion on the situation. Here is a puzzling problem and for its solution the efforts of many minds will be needed. Perhaps the Committee can be of help in formulating a workable plan for better clinical testing.

It is satisfying that the Committee on Public Health has an illustrious past, but what is more stimulating is to realize that it has a promising future. By Chinese standards it is entering its period of glory.

A tourist riding past the government archives building looked at the motto engraved on it. It read: "What is past is prologue." Nonplussed, the tourist asked the cab driver what it meant. "It means", said the driver, "that you ain't seen nothin' yet."

Perhaps this thought has been more elegantly phrased by the poet:

"Man of the Future, what shall be
The life of Earth that you shall see?
What strange new facts the years will show?
What wonders rare your eyes shall know?
To what new realms of marvel, say,
Will conquering science war its way?"

NEW YORK PATHOLOGICAL SOCIETY

ABSTRACTS OF PAPERS AND DISCUSSION

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*The Effect of Bacterial Endotoxin on the Blood-Vascular System**

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These studies of the effects of bacterial endotoxin were prompted by the observation at autopsy that certain human disease processes present the same tissue reactions as do experimental animals who develop the generalized Shwartzman reaction.[1] The hope has been that an understanding of the mechanisms involved in the animal experiments might lead to a better understanding of the diseases occurring in man.

The intravenous injection of relatively small amounts of bacterial endotoxin (0.2 mg.) into rabbits results in the deposition of thrombi which coat the walls or occlude the lumens of small vessels in the liver, lungs and spleen. The rabbit usually survives this exposure, but if a second injection is given 24 hours later, 60 to 80 per cent of the animals develop thrombi in the renal glomeruli. If the animal survives, symmetrical cortical infarction of the kidney occurs within another 24 hours due to the cessation of blood flow through the glomeruli.

We have addressed ourselves to two questions raised by these observations: (a) What is the nature of the thrombotic material? And (b) What is the mechanism that causes this material to deposit in the sites of predilection; more particularly, why are the glomerular capillaries involved after two exposures to endotoxin and not after one exposure?

The first question was approached by studies of the blood coagulation mechanism during the generalized Shwartzman reaction.[2, 3] The observations that heparin prevented the generalized Shwartzman reaction[4, 5] suggested that the thrombi were composed of fibrin. It was noted that 24 hours after the first injection of toxin the fibrinogen level rises to twice the normal values. The second injection at this time causes a 30 to 40 per cent decrease in fibrinogen content in four hours. Twenty hours later it again rises to twice the normal values. The decrease in circulating fibrinogen coincides with the appearance of the thrombi in the glomeruli and suggests that these thrombi are derived from the circulating fibrinogen. Other changes were found in the coagulation system. A marked decrease in whole blood coagulation times in silicone occurred four hours after both injections, but rose to normal values 24 hours after each injection. The circulating platelets dropped from average levels of 300,000/c.mm. to 150,000/c.mm. after the first injection. The platelets remained at this low level and decreased to less than 100,000 after the second injection. During this time no fibrinolytic or fibrinogenolytic activity could be demonstrated. It has also been shown that the hypoprothrombinemic drug sodium warfarin will prevent the generalized Shwartzman reaction[6] as well as the induction of fibrinolytic activity at the ap-

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propriate time.[7] Finally, it has been shown by use of the fluorescent antibody technique that the intravascular deposits are immunochemically identical with fibrin,[8] and electron microscope studies reveal that the deposits contain a fibrillar material with a periodicity identical with fibrin.

From these observations it has been concluded that bacterial endotoxin produces damage by causing disseminated intravascular coagulation, and in the case of the generalized Shwartzman reaction it is two episodes of disseminated intravascular coagulation.

However, this does not explain the qualitative difference between the two injections of toxin, namely, the localization of fibrin thrombi in the renal glomeruli only after the second injection. This is our second question, and stated in another way the problem centers around the question of what constitutes "preparation" for the generalized Shwartzman reaction.

Several studies have indicated an influence of endotoxin on the vasomotor activity of small blood vessels. Zweifach and Thomas[9] have shown several changes in the small mesenteric vessels of the rat after exposure of the blood stream to massive (lethal) doses of bacterial endotoxin. Some of these studies have suggested that endotoxin induces spasm of arterial vessels. Others have suggested that capillary or venular dilation occurs. Whether either or both of these reactions take place, a marked redistribution of blood in the various viscera could be anticipated in the generalized Shwartzman reaction. To elucidate this point a study of the distribution of India ink injected into the circulation during the course of the generalized Shwartzman reaction was done.[10]

Large ischemic areas appeared in the lungs. These were caused by arterial platelet thrombi, and possibly by arterial vasospasm. Alternating with the ischemic areas were blackened patches in which the alveolar capillaries were dilated and had trapped large amounts of ink. Four hours after each injection of endotoxin there was a virtually complete exclusion of ink from the center of all hepatic lobules. This obstruction to blood flow in the liver was associated with a dilation of the peripheral sinusoids of the hepatic lobules. No alteration was noted in the kidney until two to four hours after the second injection. At this time the glomerular capillaries dilated and filled with ink. This stasis of blood in the glomerular capillaries preceded and was concomitant with the intravascular deposition of fibrin in the same locations. It is suggested that dilation and stasis of blood in the renal glomeruli may constitute the major mechanism of "preparation" in the generalized Shwartzman reaction.

Subsequent studies have shown that the renal glomerular dilation occurs after one injection of endotoxin when the animal is "prepared" by cortisone,[11] thorotrast[12] and pregnancy.[13] The problem remaining to be answered is the mechanism of the glomerular dilation. Our present studies are directed toward learning the effects of certain vasomotor active substances on the glomerular capillaries.

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DISCUSSION

HANS POPPER: This was an excellent demonstration of the effects of fibrin thrombi which we meet quite often in human pathology under various circumstances. I wonder whether one could experimentally separate the effect of the development of fibrin thrombi from the dilation by giving heparin. To my knowledge, it has been attempted a good while ago by the Minnesota Group, to prevent the renal lesion by giving heparin. I wonder if you have done any heparin injection under these circumstances.

DONALD G. McKAY: We have not done that. We have felt that the fact that the thrombi appeared secondary to the dilation meant that the dilation did not occur as a result of the thrombosis and that it was, therefore, independent of the thrombosis, but I think this is a good idea. There is one question that I would ask. It seems to me that there is some evidence that heparin may affect the reactivity of blood vessels too, but as we haven't tried it we do not have an answer.

ALFRED A. ANGRIST: Is this localization that we see secondary in the kidney of the rabbit paralleled in other species, because rabbits are so prone to such phenomena in the kidney? This may be a very elementary question, but have you observed the lungs under direct observation to determine that spasm doesn't determine the distribution of the dye? Can you explain the variation on that basis rather than on stasis alone?

D. G. McKAY: No, I don't think we have ruled out spasm in either the kidney or the lung. There are thrombi in the small arteries of the lung, so it could well be that some of the "ischemic" areas are the result of these thrombi, but we did not find thrombi in relation to all the so-called "ischemic" areas, and we did not do serial sections, so we could not rule out the possibility of spasm. Secondly, the idea that spasm may be occuring in the kidney first, prior to the dilation, has not been excluded. One would have to study specifically, I suppose, the precapillary arterioles with some other kind of injection medium or some other technique in order to rule out this possibility. On the other hand, we did not get death of tissue without thrombosis.

ALFRED A. ANGRIST: The rat or some other animal is not so prone to this phenomenon. I wonder if there is any variation.

DONALD G. McKay: There is variation. It used to be stated that you couldn't get the generalized Shwartzman reaction in any other animal but the rabbit. On the other hand, it has been produced. I believe Brunson produced the generalized reaction in rats by first radiating them, giving total body radiation. It has also been produced in rats by first giving them a nephrotoxin nephritis and then this lesion appeared superimposed on the nephrotoxic nephritis. So the question is whether spasm, or the condition of the animal on the basis of other factors, is important.

PAUL KLEMPERER: I would like to make just this one remark. In the condition, I do not know the name any more, I call it Moschcowitz disease, there is one thing that always stands out, and that is that the small arterioles are always extremely dilated, a feature which I cannot account for, but this is everywhere. This, in human pathology, may be in support of the idea.

H. H. ZIMMERMAN: Dr. Klemperer, I think the term Moschcowitz disease is still used and still considered acceptable. Dr. McKay do you want to comment on the remarks made by Dr. Klemperer?

DONALD G. McKAY: No, but I think that is an interesting observation.

JOHN W. BERG: What might be the significance of endothelial damage in these lesions? I bring this up because similar thrombi occur in nephrotoxic nephritis and it is known that these thrombi are also fibrin, as can be shown by staining reaction and electron microscopy. Now thrombosis in nephrotoxic nephritis is preceded by endothelial damage of the capillaries, very often by dilation of capillaries. Is there anything like that in the generalized Shwartzman phenomenon?

DONALD G. McKAY: Certainly, if you try to reason and carry over the information you get from local Shwartzman reaction, you would say that there is a good chance this might be endothelial damage, and I don't think this has been ruled out. We can say, with respect to the generalized reaction, that no studies have as yet clearly shown alteration in the endothelium. Now this does not mean that an invisible change, in relation to the wetting or non-wetting property of the endothelium, might not be taking place either on a physiochemical basis or on an electrical potential basis or on the basis of stickiness, perhaps. It could well be. But Drs. Thomas and Pappas attempted to analyze this potential change or future change in the endothelium by examination by electron microscopy and they were unconvinced that there was any change in these renal vessels, particularly prior to the lodgement of the thrombi. They did find some big vacuoles that were adherent to some of the endothelial cells but they stated that they found these under other conditions and they could not attribute it exclusively to bacterial endotoxin. There is no histochemical alteration that I know of, so that all the methods that have been used so far have not shown such alteration of the endothelium in terms of anatomy; but in terms of physiology, we can't rule it out.

ALFRED ANGRIST: I have one other question. I am particularly interested in the group of animals that failed to "cooperate". Have you noticed any particular correlation there at all, particularly any changes in the adrenals in that group? And I must indulge in a general comment, if I may. It is nice to see and hear that experimental pathology can start at autopsy observation and then be brought back to it!

DONALD G. McKAY: Unfortunately we haven't studied the adrenals in these animals. The question you ask is a sort of sixty-four dollar question. If we knew the answer to that we would probably have the answer to the Shwartzman reaction. These animals were all treated the same but did not respond in the same way.

JOHN K. LATTIMER: What has your thinking been in regard to the four-hour lag period?

DONALD G. McKAY: I think at the moment it simply stands as an observation. I believe that the evidence thus far is that the bacterial endotoxin, itself, is taken up by either the reticuloendothelial cells or leukocytes of the blood within a half-hour after it gets into the circulation, so that the four-hour lag period does mean this to us, that the endotoxin has acted to produce a secondary response in the organism which then results in the major number of changes which take place either in the blood clotting system or in the vascular response. I think that beyond this rough idea of a one-two punch, we could not go with respect to the timing.

Recent Study on the Pathology of Hyperparathyroidism

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In 1953, on the basis of a series of twenty-five cases, we described the pathological anatomy of the parathyroid glands in hyperparathyroidism.[1] Primary hyperparathyroidism, we wrote, was caused by a single adenoma in most of the cases, by two adenomas in a few and in a still smaller group by diffuse water-clear-cell hyperplasia involving all four glands. Secondary hyperparathyroidism, usually due to chronic renal disease, was associated with hyperplasia of the chief-cells in all the parathyroid tissue.

Another cause of primary hyperparathyroidism is carcinoma of the parathyroid gland.[2] This extremely rare condition can often be suspected by the surgeon who finds the parathyroid tumor adherent to the surrounding tissues and sometimes to the esophagus. Microscopically, the cells are arranged in a trabecular pattern, and mitoses and stromal fibrosis are often present. Large cells with macronuclei are far more typical of benign adenomas and should not be used as a criterion for the diagnosis of cancer.

In 1952, we encountered our first case of primary hyperparathyroidism in which all four glands were replaced not with water-clear-cells but with chief-cells. In other words, the chief-cell hyperplasia that we had hitherto always connected with secondary hyperparathyroidism was now associated with primary hyperparathyroidism. Since that time we have seen ten examples among the last sixty patients with primary hyperparathyroidism. Grossly, the glands were enlarged and often nodular, with obvious fibrous septa between islands of hyperplasia. From a morphologic point of view the condition is indistinguishable from secondary chief-cell hyperplasia and in many cases resembles a single adenoma. In fact, such cases in the past had been diagnosed as multiple adenomas.

The role of the pathologist in aiding the surgeon in the operating room is thus more difficult today. In the past the finding of chief-cells on a frozen section of an enlarged parathyroid gland was always interpreted as indicating an adenoma, and since in 80 per cent of the cases hyperparathyroidism is caused by a single adenoma, the surgeon ordinarily did not explore further. Now the prudent surgeon identifies a second parathyroid gland. If the latter is normal, further exploration is usually unnecessary, but if it is enlarged and composed of chief-cells it may be a second adenoma, but probably is involved by diffuse chief-cell hyperplasia, rendering exploration of all four glands mandatory. Relief of the condition is usually attained by the removal of three glands in entirety and a portion of the fourth.

The relation of primary chief-cell hyperplasia to multiple endocrine tumors, such as islet-cell tumors of the pancreas and pituitary tumors in patients with acromegaly, was discussed, and the familial incidence of the disease in some of the cases was pointed out. The frequent occurrence of peptic ulcer and acute or chronic pancreatitis in association with primary hyperparathyroidism was also demonstrated.

In a recent paper on this subject[3] I expressed my opinion of the differentiation of the two types of hyperplasia as follows: "Is this hyperplasia really a separate entity from the water-clear-cell hyperplasia or is one a variant of the other? We believe that both types of hyperplasia are different forms of the same process. If compared to the two forms of goiter commonly associated with hyperthyroidism, the uniform microscopic appearance of the

water-clear-cell hyperplasia indicates that it may be analogous to the primary thyroid hyperplasia of Graves' disease, whereas the uneven nodular character of the chief cell enlargement may be the equivalent of the nodular goiter."

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DISCUSSION

H. M. ZIMMERMAN: I think I must call on Dr. Jaffe to open the discussion as this address was directed specifically at him and incidentally at us.

HENRY L. JAFFE: I really haven't anything to add to what my friend has presented. Two points that I would remark on, first, those cases of primary chief-cell hyperplasia versus the water-clear-cell type of hyperplasia, and I am inclined to agree with him that one is merely a phase of the other. What I would like to have seen proved or established on the basis of the large experience that they have at Massachusetts General, is a general statement to the effect that about 50 per cent of the cases show no bone changes. Now that is, no bone changes, I surmise, by x-ray findings. I wonder whether the surgeons at Massachusetts General are ambitious enough to take a sliver of the sternum out and subject it to histologic studies and whether, if that were done, they would persist in claiming that a hot, functioning parathyroid, which had been functioning for some time, would leave the spongy trabeculae completely untouched.

B. CASTLEMAN: We have had a few bone biopsies and I haven't been able to find any evidence of bone resorption. The alkaline phosphatase is normal in these cases and I know that Dr. Gordon in San Francisco thinks he can find changes. Have you seen any in some of these cases, Dr. Jaffe?

HENRY L. JAFFE: No, I haven't followed that point.

H. M. ZIMMERMAN: Dr. Jaffe, would you tell Dr. Castleman what bones he should study?

HENRY L. JAFFE: That is simple. Take the ribs, the vertebral column or the calvarium. I think the point that Dr. Castleman made about the osteoid zone is very interesting. You can treat an animal with parathormone, then take the animal off parathormone and the serum calcium drops, and this animal may sometimes go into tetany. The bones act like a vacuum to suck up a great deal of the circulating calcium.

What has happened to the large nonfunctioning acidophyllic adenomas that they used to see years and years ago, and cases of which are occasionally described in the literature? I haven't seen any.

B. CASTLEMAN: I have seen just one and the one described by that English surgeon some years ago when he found an incidental oxyphile adenoma.

MELVIN HOROWITZ: To complete the picture, how often do you encounter a large adenoma without functioning evidence? And then another question as a corollary, have you seen any carcinomas of the parathyroid that did metastasize to bone that gave no evidence in biochemical studies?

B. CASTLEMAN: I am unable to recognize a nonfunctioning carcinoma of the parathyroid gland, because I couldn't be sure that it wasn't a thyroid carcinoma. We are trying to devise some histochemical method that might help us; so far we have not been able to do so. I think that when one has a carcinoma that metastasizes and is nonfunctioning, I would prefer to call it thyroid carcinoma rather than parathyroid carcinoma. I wouldn't be able to tell them

apart. I am sure that there must be some parathyroid carcinomas that do not function; there is no reason why there shouldn't be, but so far I haven't been able to be sure of it.

WILLIAM D. JOHNSON: In connection with the recognition of the differentiation of parathyroid from thyroid, Dr. Klink has attempted to demonstrate glycogen in these and has done so fairly consistently with all the demonstrable parathyroid lesions. Have you attempted this?

B. CASTLEMAN: I have seen Dr. Klink's work and he is not at all convinced of the adequacy of the method himself. There are too many exceptions in his method; given an individual case, he can't be sure.

MAX WACHSTEIN: In a recent local discussion a slide was shown in which a diagnosis of adenoma of the thyroid was at first made, but after two years the patient returned with not only local recurrence but lymph node metastasis. In your examination of the slide, you were said to have stated that the presence of even one mitotic figure should indicate the malignancy of the lesion. Is that correct? Do you feel that one or two mitotic figures in an otherwise entirely benign lesion should indicate that the lesion is malignant?

B. CASTLEMAN: I have been unable to find mitoses in an adenoma, and it has turned out that in cases that have had mitoses, some of them have proved to be carcinoma. Others that we called carcinoma did not develop metastasis, so we really don't know. But if one sees mitoses in a parathyroid lesion, one should be suspicious. There are other evidences of carcinoma that might go along with it that would help make the diagnosis.

JOSEPH C. EHRLICH: I would like to say that that was my case. I sent the slide to Dr. Castleman, but I sent him not only the slide of the adenoma but also the slide of the metastasis at the same time. At that time he wrote that the tumor that we called a parathyroid adenoma was obviously a carcinoma. He gave several reasons, one of them being that mitotic figures were present.

B. CASTLEMAN: In addition there was a lot of connective tissue scarring throughout, and a pattern that looked more like a carcinoma.

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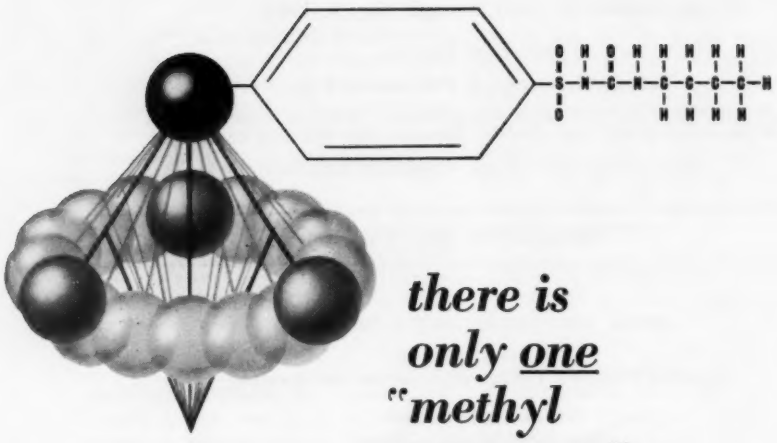

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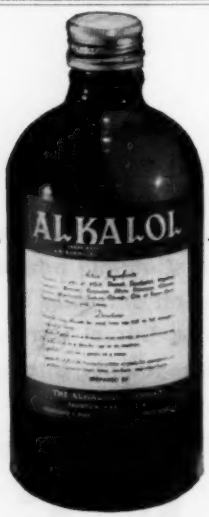

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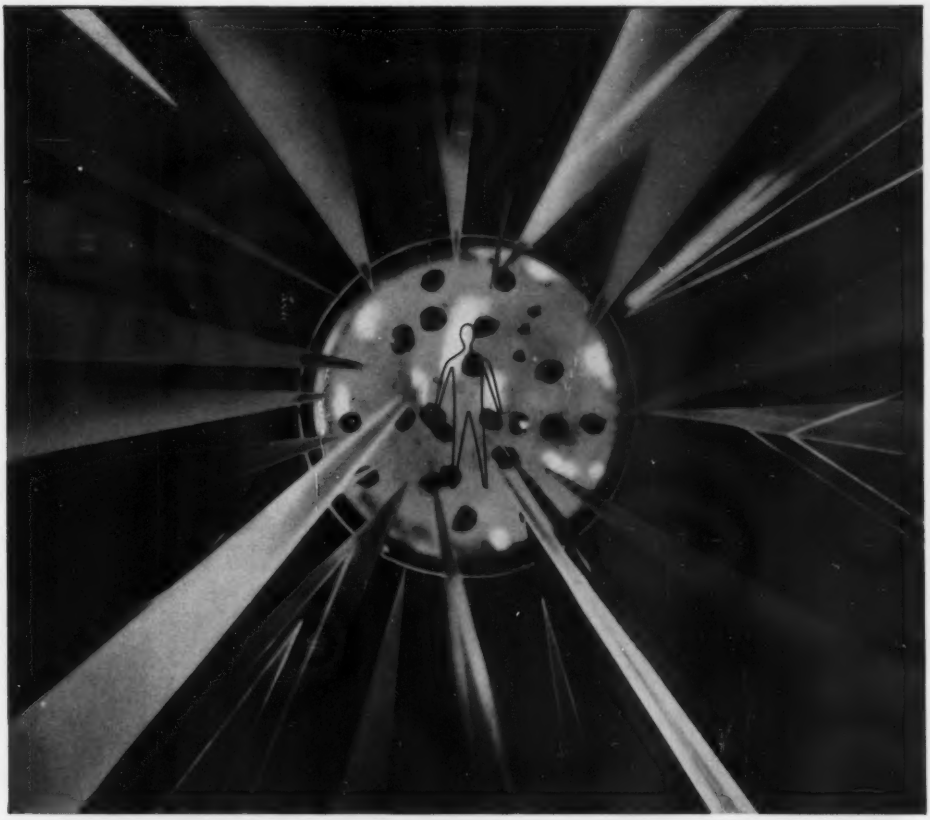

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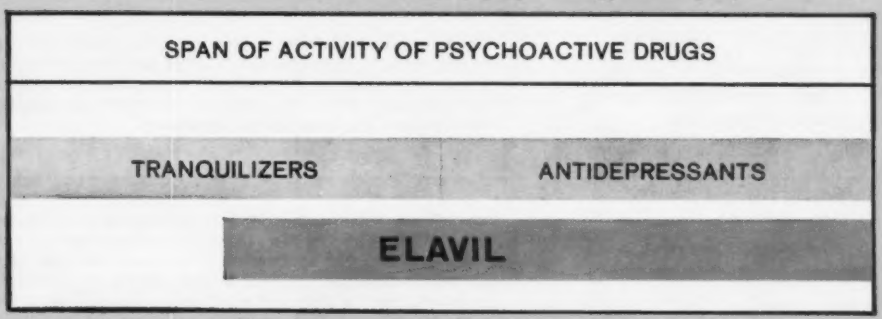

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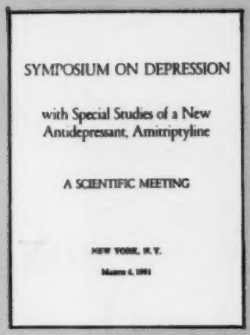

EXCERPTS FROM A SYMPOSIUM ON DEPRESSION

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INVESTIGATOR	FINDINGS
DUNLOP, EDWIN: The treatment of depression in private practice.	"Amitriptyline [ELAVIL] has a specific advantage over any antidepressant currently available and I see increasing evidence of its usefulness in reducing tension, agitation and anxiety, as well as in relieving the depressive quality of the illness. Amitriptyline appears ... to combine better than any other antidepressant drug the successful treatment of anxiety at one end of the scale and depression at the other. Experience in the past has shown us that, when using electroshock or analeptics, although depression can be relieved, the accompanying anxiety eventually proves more troublesome than the depressive phase of the illness. Amitriptyline successfully bridges these divergent symptoms which are displayed in varying proportions in all depressive syndromes. "... Approximately one hundred and twenty patients have been studied with amitriptyline during the last fifteen months. It is an effective antidepressant when employed in both hospital and ambulatory patients. Its dependability and freedom from toxicity and severe side effects merit further evaluation on a broader spectrum of depressive disorders."
BENNETT, DOUGLAS: Treatment of depressive states with amitriptyline.	"In those cases showing a good response, early and dramatic improvement in sleeplessness resulted and many patients noted a feeling of relaxation. The ability of some patients to reduce their night sedatives after only a month's treatment was unique in my experience of the treatment of depression."
SAUNDERS, JOHN C.: Antidepressives: the pith of affective therapy.	"Its primary action in hospitalized psychotics is antidepressive; this along with its very low rate of side actions make it a drug of potentially frequent application in a broad spectrum of neuropsychiatric diseases.... Since a large part of any hospital population will reach a plateau if given only a tranquilizer or an energizer, we suggest that amitriptyline alone be given prior to combination therapy, as this drug is easier and safer to administer and produces a significant improvement in a high percentage of cases (60-75)."
OSTFELD, ADRIAN M.: Effects of an antidepressant drug on tests of mood and perception.	"Finally, it appears that amitriptyline in the doses employed here is relatively effective in depressed states of neurotic proportions. Its freedom from severe side effects in doses that are therapeutically effective seems established in this patient population."

(This symposium was published in Diseases of the Nervous System, Volume 22, Section Two—Supplement, May 1961)

INVESTIGATOR	FINDINGS
AYD, FRANK J., JR.: A critique of antidepressants.	"Amitriptyline and imipramine induce similar side effects but, generally speaking, those of amitriptyline cause less subjective discomfort in patients than those of imipramine. "... Many of the factors that favor a satisfactory response to these drugs are also those clinically associated with the expectation of a good reaction to ECT. The danger lies in their general slowness in taking effect which makes their use hazardous for severely depressed suicidal patients who, preferably, should be treated with electroshock therapy. Otherwise, these compounds can be a satisfactory substitute for shock therapy for most depressed patients. Thus, these drugs have lessened the need for ECT. On those occasions when ECT is necessary, if the shock therapy is combined with an antidepressant, ECT can be dispensed with after a few treatments."

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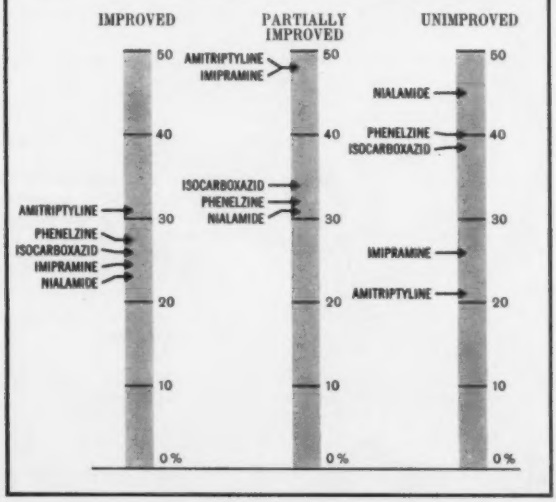

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EXCERPTS FROM A SYMPOSIUM ON DEPRESSION (continued)

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INVESTIGATOR	FINDINGS
DORFMAN, WILFRED: Masked depression.	"In evaluating the effectiveness of amitriptyline in all these different settings, it was considered to be effective in 17 of the 25 patients (68%)."
FELDMAN, PAUL E.: Psychotherapy and chemotherapy (amitriptyline) of anergic states.	"Compared to other energizer compounds, particularly the hydrazines, amitriptyline appears to be relatively nontoxic. The laboratory reports for the most part remained within normal limits. Occasionally, abnormal readings were reported, but these appeared only sporadically and were not related to any clinical findings."

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REFERENCES: 1. Ayd, F. J., Jr.: Psychosomatics 1:320, Nov.-Dec. 1960. 2. Dorfman, W.: Psychosomatics 1:153, May-June 1960. 3. Barsa, J. A., and Saunders, J. C.: Am. J. Psychiat. 117:739, Feb. 1961.

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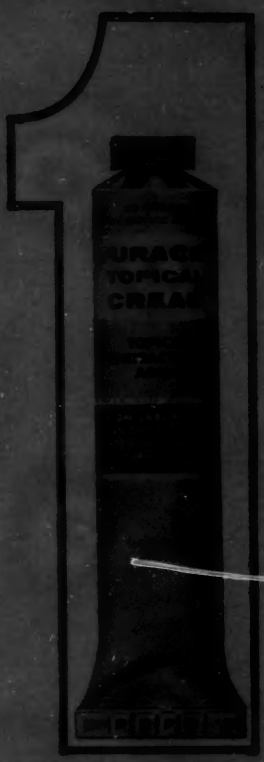

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